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EXPERIMENTAL PRODUCTION OF GALLSTONES BY INCOMPLETE STRICTURE OF THE TERMINAL COMMON BILE DUCT

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NUMEROUS experimental inquiries have been made into factors responsible for formation of concretions in the biliary system. Early investigators, among others, Gilbert (1898),[8] Mignot (1898),[11] Cushing (1899),[7] and Wilkie (1928)[18] emphasized the role of infections in the genesis of cholecystitis and cholelithiasis. Naunyn (1921),[12] Aschoff (1924)),[1] and Aschoff and Bacmeister (1909),[2] earlier strong proponents of the inflammatory origin of gallstones, later inclined to a more complicated origin, involving inflammatory, metabolic, and stasis factors. Stasis as a factor in biliary tract disease was stressed by Berg (1922).[3] Homans (1897)[10] related an instance of gallstone formation in man following placement of silk sutures attending the performance of cholecystostomy 20 months previously. The role of variations in the composition of bile and metabolic alterations in the causation of gallstones have been pointed out by Rous and his associates (1924)[15] in a number of papers. Reflux of pancreatic juice into the common bile duct as a cause of cholecystitis was proposed by Wolfer (1931).[19] Hjorth (1947)[9] injected active trypsin into gall bladders of rabbits with accompanying ligature of the cystic duct and succeeded in producing cholecystitis quite regularly and concretions occasionally.

The frequent observation at operation in this clinic, that patients with cholelithiasis often were found to have an abnormal degree of narrowing of the common duct at its terminus, led to routine exploration and examination of the biliary ampulla when cholecystectomy was indicated for cholelithiasis,[16] a procedure which has been standard practice on the surgical service of one of the authors for 3 years. With the terminal common bile duct elevated upon

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a small probe introduced through the cystic duct, the ampulla is located readily under direct vision and graduated probes are passed through the ampulla to measure its size. A review of the records of 50 patients who have had an inspection of the sphincter of Oddi in this manner at the time that cholecystectomy was performed for cholelithiasis disclosed that in 29 (58 per cent) of these narrowing at the ampulla was such that a 3 mm. probe (smallest Bakes' dilator) could not be passed into the duodenum through the sphincter. In fact a pin-point opening of the ampulla into the duodenum is not an uncommon finding when duodenotomy is done regularly when cholecystectomy is undertaken for gallstones.

AUTOPSY OBSERVATIONS

Evidence concerning the size of the biliary ampullary opening in subjects with and without stones in the biliary system was obtained during routine autopsies with the help of the Department of Pathology. The study involved observations concerning the extrahepatic biliary tract of 28 patients ranging in age from 9 to 82 years. Concretions were present in 6 of the subjects. In 2, the ampulla of Vater would allow passage of a probe no larger than a No. 3 Bakes' dilator. The orifice of the papilla in a third patient was pin-point in size. A fourth had obstruction of the common bile duct by tumor with formation of small stones proximal to the point of obstruction. The fifth had stones present only in the gall bladder, with the cystic duct in this instance narrowed almost to the point of complete obstruction. The common bile duct of the sixth patient of the group with stones was not narrowed at the ampulla; a No. 5 Bakes' dilator could be passed with ease. Thus, partial obstruction of the biliary tree distal to the site of stone formation could be demonstrated in 5 of 6 patients with gallstones.

In 22 instances in this series no gallstones were found in the biliary tract at autopsy. A small opening of the biliary papilla was observed once, the sphincter barely admitting passage of a No. 3 Bakes' dilator. In two instances a No. 4 Bakes' dilator passed readily. In the remaining 18 patients, it was possible to pass a No. 5, 6, or 7 Bakes' dilator.

TABLE I. AUTOPSY OBSERVATIONS ON SIZE OF PAPILLA OF VATER

GALLSTONES PRESENT		GALLSTONES ABSENT	
SIZE OF BAKES' DILATOR THAT READILY PASSED THROUGH PAPILLA	NUMBER OF PATIENTS	SIZE OF BAKES' DILATOR THAT READILY PASSED THROUGH PAPILLA	NUMBER OF PATIENTS
< 3	1	< 3	1
3	2	3	–
4	–	4	2
5	2*	5	8
6	–	6	7
7	–	7	4
8	–	8	–
9	1†	9	–

*Gallstones present only in gall bladder of one of these; cystic duct almost completely obstructed by fibrosis.

†Common bile duct obstructed by tumor. Proximal to it were present both gall-bladder and common bile-duct stones.

EXPERIMENTAL OBSERVATIONS

The experiments reported below were designed to test the thesis that gallstones might be produced by a relative stenosis at the ampulla. The results indicate that under the conditions of the experiment, narrowing of the terminal common duct may be followed by the appearance of gallstones in the gall bladder and in some instances in the common bile duct, an occurrence which suggests that narrowing at the ampulla may be an agency in gallstone formation in man.

Method.—Several animal species have been utilized, including the dog, rabbit, and monkey. Animals were operated upon under pentobarbital anesthesia using aseptic technique. After exposure of the common bile duct at its site of entrance into the duodenum, a small strip of cellophane sealing tape, dusted lightly with dicetyl sodium phosphate, was sutured very loosely around the terminal common bile duct just before it penetrated the duodenal wall (Fig. 1). The property of this substance to stimulate fibrosis is well known. No other manipulation of the extrahepatic biliary system was carried out, and the abdomen was closed with interrupted sutures of fine silk.

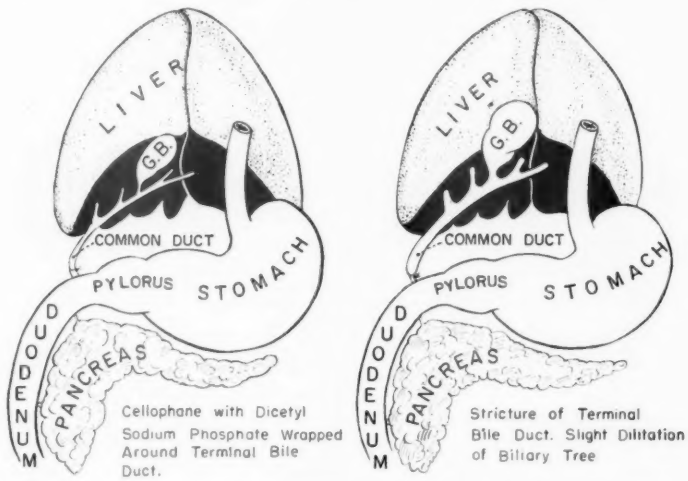
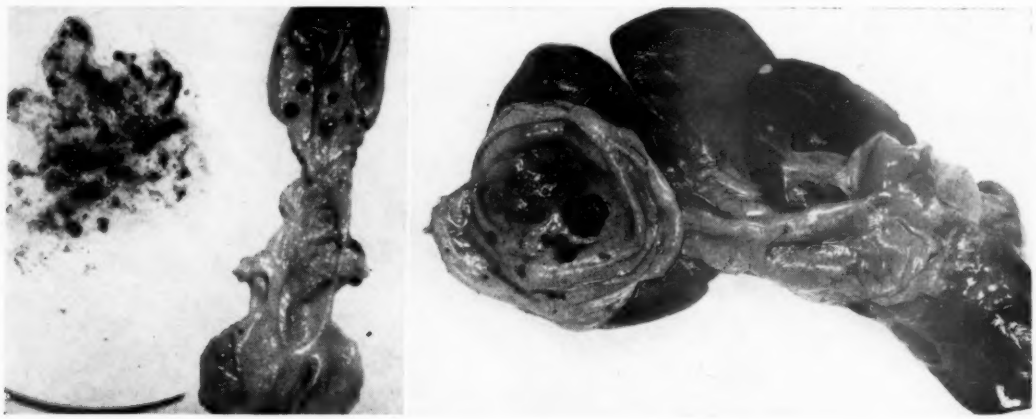


Fig. 1.—Experimental technique utilized to produce partial obstruction of common bile duct with fibrosing agent.

Animals received no special postoperative care and were fed regular laboratory rations. All animals that died were autopsied; the others were sacrificed at varying intervals of time. The extrahepatic biliary passages, gall bladder, and liver were examined and particular attention was given to the degree of narrowing of the bile duct at the site of application of the stenosing agent, the extent of dilatation of the bile ducts and gall bladder, the character of the contents therein, evidence of jaundice, and appearance of the liver. A few stones were analyzed qualitatively for calcium, bilirubin, and cholesterol content. In several animals, cultures of bile were made under aerobic and anaerobic conditions at the time of sacrifice. In several living rabbits radiographic studies have been carried out with the intent of visualizing the

stones. Iodopanoic acid in doses of 0.5 to 1.5 Gm. orally and iodipamide methylglucamine (38.4 per cent) in doses of 2 to 20 ml. intravenously have been utilized.

Results.—At autopsy there was usually considerable fibrosis in the area of the common bile duct to which the reactive cellophane had been applied. If the common duct was only narrowed, but patent to the passage of a 1 mm. probe or to bile, the stricture was classified as incomplete. If a 1 mm. probe could not be passed through the narrowed area and bile could not be squeezed through readily, the obstruction was classified as complete. In incomplete stricture, the gall bladder and common bile duct were dilated slightly or moderately. The liver appeared normal and there was no jaundice. Stones occurred in both the gall bladder and common duct, but more commonly in the gall bladder. If complete stricture resulted from application of the reactive cellophane ligature, the biliary tree was usually greatly dilated and the liver appeared swollen and was yellow in color. Other viscera showed evidence of obstructive jaundice as well, with varying degrees of bile staining.



A. *B.*

Fig. 2.—Extrahepatic biliary tree and gallstones from (*A*) dog and (*B*) rabbit with experimental stricture of distal common bile duct.

In Table II are shown the results obtained with incomplete stricture of the terminal common duct in the 3 species studied. The extrahepatic biliary tracts and stones from a rabbit and a dog are shown in Fig. 2. Stones occurred in a rabbit as early as 3 weeks following application of the stenosing agent around the duct. They were present in dogs autopsied at 7 and 20 weeks after operation. Gallstones were found in one monkey autopsied at 19 weeks.

TABLE II. STONES IN BILIARY TRACT FOLLOWING EXPERIMENTAL STRICTURE OF TERMINAL COMMON BILE DUCT
(Incomplete Stricture)

SPECIES	NUMBER OF ANIMALS	NUMBER WITH STONES	LENGTH OF OBSERVATION (WEEKS) BEFORE DEATH OR SACRIFICE
Rabbit	8	7 (87%)	4-16 (Mean 9)
Dog	8	2 (25%)	4-20 (Mean 8)
Monkey	2	1 (50%)	19-22

Complete obstruction of the common duct obviously was not the result desired in the experiment, but did occur in several animals (Table III). One rabbit with complete stricture developed stones; in the remainder of animals with complete biliary obstruction, stones were not found. It appeared that narrowing but not total obstruction to the duct provided the optimal situation for stone development.

TABLE III. STONES IN BILIARY TRACT FOLLOWING EXPERIMENTAL STRICTURE OF TERMINAL COMMON BILE DUCT

(Complete Stricture)

SPECIES	NUMBER OF ANIMALS	NUMBER WITH STONES	LENGTH OF OBSERVATION (WEEKS) BEFORE DEATH OR SACRIFICE
Rabbit	1	1	6
Dog	2	0	5, 10
Monkey	2	0	6, 11

Serum bilirubin values were determined in 7 rabbits in the late postoperative period (Table IV). The common duct of each of these animals was incompletely obstructed at autopsy. Only one of the 7 showed a slight elevation of serum bilirubin and none appeared jaundiced. Stones were present in the biliary tree in all.

TABLE IV. SERUM BILIRUBIN VALUES IN RABBITS WITH EXPERIMENTALLY PRODUCED BILIARY STONES

(Incomplete Obstruction of Terminal Bile Duct)

ANIMAL NUMBER	WEEKS POSTOPERATIVE	BILIRUBIN (MG. %)	
		ONE MINUTE	TOTAL
2	3	0	0.1
3	10	0	0.1
5	14	0.4	0.5
6	15	0.1	0.2
7	4	0	0.1
8	5	0	0.1
9	4	0	0.1

Stones from 9 animals have been analyzed for composition. Specimens from 2 rabbits were bilirubin stones; those from 4 rabbits were mixed bilirubin-cholesterol concretions. Stones from 2 dogs and the monkey in which the presence of calculi was observed were combination stones of bilirubin-cholesterol composition. Calcium was not found in any of the stones formed in experiments reported here. Pure bilirubin stones were very soft and crumbled readily on slight pressure; those stones containing cholesterol as well were much more firm but could be crushed between the fingers. None of the stones had the extreme hardness sometimes seen in human biliary concretions.

Aerobic and anaerobic cultures of the bile from 6 rabbits with stones were made at the time of sacrifice. Cultures from 5 of these were sterile. A gram-negative bacillus, present in only one medium inoculated with bile from the sixth animal, was thought to be a contaminant. *Escherichia coli* was grown from the bile obtained from the biliary tree of a rabbit studied bacteriologically wherein no stones were present at autopsy.

Radiographs taken at intervals of 2 to 24 hours after oral administration of 0.5 to 1.5 Gm. of idopanoic acid to 4 rabbits have not demonstrated the biliary tree and contained stones, and x-ray studies at intervals from 15 minutes to 4 hours after intravenously administered iodipamide methylglucamide have likewise not shown the extrahepatic biliary tree and contained stones in 4 rabbits studied.

DISCUSSION

Experimental production of a degree of biliary stasis by the utilization of dicetyl sodium phosphate around the terminal bile duct will result in the formation of stones in the gall bladder and the bile duct even when the bile remains free of bacteria. It would appear that partial obstruction to the outflow of bile, as might occur with narrowing or fibrosis of the sphincter of Oddi, sufficient to provide a degree of stasis, yet not great enough to produce manifest icterus, is a likely and important cause of biliary stones in man. Our observations would suggest quite definitely that infection is not a necessary component of gallstone formation.

In examining the literature in preparation for publication of this paper, we ran across the work of Westphal and his associates[17] of Hanover, Germany, published more than 25 years ago. These important papers were unknown to us. In Volume 115 of *Zeitschrift für klinische Medizin* for the years 1930 and 1931, the authors published a series of 8 papers. Their fifth paper is particularly pertinent to this discussion. In this publication, Westphal and Gleichmann report a series of operations on dogs in which they obstructed the cystic duct by ligature in one series (Group I); in another, they established an incomplete ligature of the mid-portion of the common bile duct, effecting the obstruction with catgut which had been dipped in hot saline solution. Their experience was that the catgut dissolved in a few days and that the continuity of the bile duct was re-established (Group II). In a third series of dogs a complete ligature of the terminal common bile duct just proximal to the point of entry into the duodenum was made. In a few dogs, in all the categories of the experiment, the authors injected bacteria or fine suspensions of charcoal. Some of the animals were sacrificed in a few days. In some of these, what the authors described as a "bilirubin fall-out" could be observed. In experiments of longer duration in Group II in which incomplete ligature of the common bile duct had been established, stones in the gall bladder formed in several instances; in the majority, however, bacteria were isolated from the biliary passages at the time of sacrifice.

Bisgard and Baker (1940)[4] established temporary incomplete, and long-standing complete obstructions of the bile duct in the goat. In some experiments, the authors ligated the common bile duct above the point of entry into it of the duct of Wirsung; in others, the ligature was placed upon the common bile duct in the supra-ampullary region below the entrance of the pancreatic duct, thus permitting reflux of pancreatic juice into the gall bladder. In experiments in which Bisgard and Baker ligated the common bile duct above the point of entry of the pancreatic duct, the gall bladder was little changed

and no stones were observed. In 5 of the experiments the obstructing ligature was placed low upon the common duct permitting the reflux of pancreatic juice into the biliary system; in 3 of 5 such experiments, the authors observed the production of gallstones. They concluded that the reflux of pancreatic juice into the gall bladder was a necessary component in the production of gallstones. Bacteria were recovered from the gall bladder in all 3 instances.

Clinicians have held largely to the view that disturbances of the sphincter of Oddi represented an end result of gallstone formation. The present studies, on the contrary, suggest quite definitely that anatomic narrowing of the terminal common bile duct is more likely a precursor of gallstones. Longstanding partial obstruction of the common duct from stenosis at the sphincter of Oddi has been implicated by Cattell and associates (1957)[5] as responsible for some instances of stone formation in the common bile duct.

In the thesis herein postulated, that anatomic narrowing of the sphincter of Oddi or stenosis of the biliary papilla is the cause of gallstones, the cause of the narrowing, in turn, needs elucidation. Repeated periods of spasm of the sphincter in themselves have been proposed as the forerunner of narrowing of the biliary sphincter. This occurrence, however, is still demanding of objective experimental demonstration. If the narrowing responsible for the settling out of bile pigment, which in turn eventuates in gallstone formation, is at the terminus of the papilla, the reflux of pancreatic juice invoked by Bisgard and Baker obviously could be regarded as a causative agency. More recently, in this laboratory, observations upon the sensitivity of the mucosa of the bile duct to perfusion with gastric juice have been assessed (Yonehiro and associates,[20] 1957). Much to our astonishment, the glandular epithelium of the bile duct appears to exhibit the same sensitivity to injury by gastric juice as does the squamous epithelium of the esophagus. In fact, gastric juice which will cause perforation of the esophagus after 2 hours of perfusion in the cat, usually also will be followed by perforation of the common duct, attending the dripping of the same juice into it. As yet, we have not had the opportunity to determine whether pancreatic juice activated by bile will injure the epithelium of the common bile duct. Such studies, obviously, need to be made. The experiments of Wolfer (1931),[19] Hjorth (1947),[9] and Bisgard and Baker (1940)[4] upon the gall bladder, employing pancreatic juice activated by bile suggest definitely that bile and pancreatic juice could produce a stenosing choledochitis. In this connection it is to be recalled that Cross,[6] from this laboratory (1951), observed that bile and pancreatic juice when admitted to the esophagus did cause hemorrhagic mucosal erosions.

Another agency which should come under suspicion, in the light of the demonstrated sensitivity of the bile-duct epithelium to gastric juice, is exposure of the bile-duct component of the papilla, as it protrudes into the duodenal lumen, to the possible damaging effect of gastric juice. This segment of the problem is under experimental scrutiny at the present time.

SUMMARY

Gallstones have been produced experimentally by causing incomplete stricture of the distal common bile duct. It is suggested that this occurrence

may have its counterpart in man and that stenosis of the sphincter of Oddi or stricture of the terminal biliary papilla may be a frequent responsible agent in the formation of gallstones in man. It has been observed in man that the presence of gallstones is associated with a high incidence of narrowing of the terminus of the common bile duct. It remains to be determined what pathologic conditions predispose to narrowing of the biliary ampulla.

Is cholecystectomy without examination of the biliary papilla by duodenotomy an incomplete operation for gallstones? It is a fair question in the light of this study. When the common bile duct is observed to be dilated at the time of cholecystectomy, it certainly would appear to be wise to have a look at the biliary ampulla. If future studies confirm and establish the sensitivity of the bile-duct epithelial component of the biliary papilla to injury by gastric juice, surgeons may have to turn to employment of isolated jejunal loops, reattached to the duodenum in the area of the biliary ampulla, as a substitute for sphincterotomy.

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EVALUATION OF THE RISK IN THE MEDICAL TREATMENT OF ACUTE CHOLECYSTITIS

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DISSATISFACTION with the medical treatment of acute cholecystitis has resulted in recommendations of early operation. Heuer,[5] Glenn,[4] and Barksdale and Johnston[1] are strong proponents of early operation in patients with acute cholecystitis. However, many surgeons recommend initial medical management with operation when the clinical manifestations of the acute attack have subsided. The proponents of delayed operation for acute cholecystitis cite the general and technical advantages of elective operation on a patient who is in a clinical remission. It is the purpose of this study to evaluate the risk of medical treatment of acute cholecystitis when this treatment is employed to produce clinical remission and then followed in most cases by elective operation.

The experiences with acute cholecystitis at the Lenox Hill Hospital from 1937 through 1953 were analyzed and form the basis of this report. Three hundred and eighty-one patients were treated by early operation, by initial medical treatment with later operation, or by medical therapy alone.

The diagnosis of acute cholecystitis was established by the following criteria. In those cases treated by cholecystectomy the histologic examination of the gall bladder was the basis of the diagnosis. In patients who had cholecystostomy, the diagnosis of acute cholecystitis was accepted on the basis of gross inspection. In patients treated medically, the criteria were acute right upper quadrant abdominal pain and tenderness, body temperature over 100.4° F., and leukocytosis occurring in a patient with known gall-bladder disease.

The cases were divided into the following clinical categories. In the first category are the patients treated by early operation. Early operation is defined as operation performed in the first 72 hours of the clinical attack of acute cholecystitis or in the first 2 hospital days.

In the second clinical category are those patients treated medically for a period longer than 2 days in the hospital and then operated upon. Some of these patients had a favorable response to medical treatment, their clinical signs of acute cholecystitis subsided, but they still had acute cholecystitis at operation. These patients are designated medical successes in that their clinical response was favorable. Other patients treated medically for more than 2 days did not have a favorable response to medical therapy, their clinical signs

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of acute cholecystitis increased, and they had acute cholecystitis at operation. These cases are designated medical failures since the clinical response was unsatisfactory.

In the final category are those patients who had acute cholecystitis and were treated medically. They were discharged from the hospital in clinical remission without operation.

MATERIALS AND METHODS

During the years 1937 through 1953, 381 cases of acute cholecystitis were treated at the Lenox Hill Hospital by all services. Two hundred and ninety patients were treated by cholecystectomy, and 28 were treated by cholecystostomy. The diagnosis of acute cholecystitis was confirmed by histologic examination in the cases where cholecystectomy was performed. Diagnosis by gross inspection was accepted in the cholecystostomy group. There were, in addition, 63 medically treated cases in which operation was not performed.

Sex and Age.—In this series there were 247 women and 134 men. The ages ranged through every decade from the second to the ninth. There were 135 patients under the age of 50, and 246 patients over the age of 50. The youngest patient was in his second decade, and there were 9 patients 80 years or over. There were 130 patients in the sixth decade.

Pathology.—In the series of 381 patients with acute cholecystitis, 318 were treated by operation. There were 300 patients with cholelithiasis, and 18 patients were noted to have noncalculus cholecystitis. Eleven patients had perforation of the gall bladder and 12 patients had gangrene of the gall bladder. Twenty patients were noted to have calculi in the common duct and 13 patients had significant elevations in serum amylase levels. (See Table I.)

TABLE I. PATHOLOGY OF ACUTE CHOLECYSTITIS

	TOTAL	DEATHS
Uncomplicated acute cholecystitis	325	14
Elevated serum amylase	13	0
Common duct stone	20	1
Perforation of the gall bladder	11	1
Gangrene of the gall bladder	12	0

Complications.—Of the 318 patients treated by operation, 42 had postoperative complications. There were 2 complications in the 63 patients treated without operation.

The most frequently recognized complications were retained common duct stone, 7; wound disruption, 9; and wound infection, 5. Eight patients had pulmonary complications of which 5 were bronchopneumonia. Two patients had cardiac complications. The effect of age upon the incidence of complications was not demonstrated in this series, for the complications rate over the age of 50 was 11.2 per cent, and the rate under the age of 50 years was 11.8 per cent. The complications rate among men was 13 per cent, and among women it was 10 per cent.

Mortality.—There were 16 deaths with an over-all mortality of 4.2 per cent. In the 135 patients under the age of 50 years, there were 4 deaths, a mortality rate of 3 per cent. In the 246 patients over the age of 50 there were 13 deaths (4.8 per cent). In the 63 patients treated without operation 4 died (6.3 per cent). In the 318 patients treated with operation there were 12 deaths (3.7 per cent). The causes of death are listed in Table II. Thromboembolism and pneumonia are the most frequently encountered causes of death in this series and represent 62 per cent of the deaths.

TABLE II. CAUSES OF DEATH

CAUSE OF DEATH	NUMBER	OPERATED	NOT OPERATED	AUTOPSY
Pulmonary embolus	5	5		2
Bronchopneumonia	2		2	1
Aspiration pneumonia	2	2		
Tuberculous pneumonia	1	1		
Coronary thrombosis	1	1		
Cardiac arrest	1	1		1
Perforated gall bladder	1		1	1
Acute hemorrhagic pancreatitis	1		1	1
Retroperitoneal abscess with common duct stone	1	1		1
Acute glomerulonephritis	1	1		
Total	16			

Grouping of Cases.—The 381 cases of acute cholecystitis were divided into clinical categories according to the type of treatment they received (Table III). In the first category are the 72 patients who had early operation within 72 hours of the onset of symptoms or within the first 2 hospital days. There were 4 deaths in this group, (5.5 per cent). There were 16 complications (22 per cent), and 10 patients had cholecystostomy (14 per cent).

In the second category are the 246 patients who had late operations after preliminary medical management of 2 days or longer in the hospital. There were 8 deaths in this group (3.2 per cent). There were 26 patients with complications (10.6 per cent) and 18 patients had cholecystostomy (7.3 per cent). (See Table III.)

TABLE III. GROUPING OF CASES AND RESULTS OF TREATMENT

	TOTAL	MORTALITY		COMPLICATIONS		CHOLECYSTOSTOMY	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Early operation	72	4	5.5	16	22	10	14
Late operation with preliminary medical treatment	246	8	3.2	26	10.6	18	7.3
Successful response to preliminary medical treatment	188	5	2.6	17	9	4	2.1
Failure to respond to preliminary medical treatment	58	3	5.1	9	15.5	14	24.1
Nonoperative	63	4	6.3	2	3		

Of the 246 patients who had late operations, 188 patients responded favorably to medical treatment; the clinical signs of acute cholecystitis subsided, and operation was done following clinical remission. This is our medically successful group and included among these cases are 10 patients readmitted as cases of chronic cholecystitis for elective operation. There were 5 deaths in these 188 patients, a mortality rate of 2.6 per cent. There were 17 complications (9 per cent) and 4 patients had cholecystostomy (2.1 per cent). (See Table III.)

The remaining 58 patients who had late operations did not respond favorably to medical treatment. They were operated upon with increasing clinical signs of acute cholecystitis. These patients are the medical failures. There were 3 deaths, a mortality of 5.1 per cent. There were 9 complications (15.5 per cent), and 14 patients had cholecystostomy (24.1 per cent). (See Table III.)

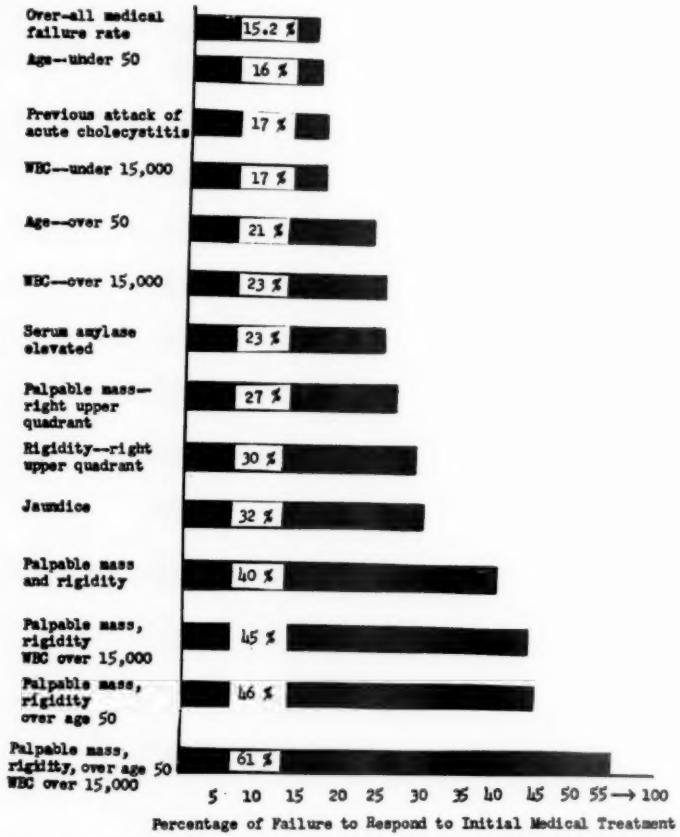

Fig. 1.—Influence of individual and combined clinical factors on response to medical treatment.

In the final category are the 63 patients who were treated without operation. There were 4 deaths, a mortality of 6.3 per cent. Two of these deaths were in patients who were moribund upon admission and although operation was planned, it could not be carried out. The other 2 deaths were mistakes in diagnosis and the patients were treated for other conditions. There were 2 complications in this group treated without operation. (See Table III.)

FACTORS INFLUENCING RESPONSE TO MEDICAL THERAPY

The influence of individual factors on the response to medical treatment was investigated (Fig. 1). It was found that age, prior history, physical findings, and laboratory examinations all had a varying influence on the response to medical therapy. In patients under the age of 50 years, 16 per cent failed to respond to medical treatment; whereas, over the age of 50 years, 21 per cent of the patients were medical failures. In cases with a prior history of acute cholecystitis medical treatment failed in 17 per cent. The physical findings of significance in medical failure were the presence of a right upper quadrant abdominal mass, right upper quadrant rigidity, and jaundice. Twenty-seven per cent of the patients with a right upper quadrant mass were medical failures. Thirty per cent of those with right upper quadrant rigidity failed to respond to medical treatment, and 32 per cent of the jaundiced patients were medical failures. In the patients with a white blood count of less than 15,000, 17 per cent did not respond to initial medical management, whereas, in patients with a white blood count over 15,000, 23 per cent did not respond.

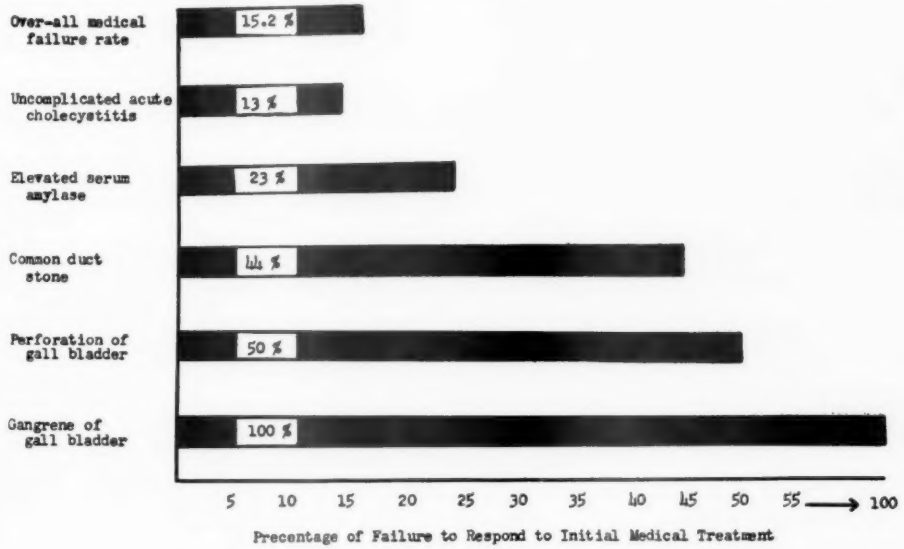

Fig. 2.—Influence of pathology on medical treatment.

When these factors were studied in combination, there is an increasing percentage of medical failures (Fig. 1). When there is a right upper quadrant abdominal mass and rigidity, 40 per cent failed to respond to medical treatment. When there is a right upper quadrant mass, rigidity, and a white blood count over 15,000, 45 per cent failed to respond. When the patient is over 50 years of age and has a right upper quadrant mass and rigidity, 46 per cent failed to respond. Finally, when a patient is over 50, has a mass, rigidity, and a white blood count over 15,000, then 61 per cent of the patients failed to respond to medical therapy.

The influence of pathology on the response to medical therapy was also investigated. Uncomplicated acute cholecystitis failed to respond to medical

treatment in 13 per cent of the cases. When an elevated serum amylase level was present, 23 per cent failed to respond. When a calculus was noted to be in the common duct, 44 per cent failed to respond. Among those patients with perforation of the gall bladder, 50 per cent failed to respond, and when gangrene of the gall bladder was present, 100 per cent failed to respond to medical treatment. (Fig. 2.)

DISCUSSION

In the treatment of acute cholecystitis a decision must be made concerning the early management of the disease. Doubilet and Mulholland,[3] Meagher and Campbell,[6] and Mustard and Custer[7] favor medical treatment with operation when the clinical signs have subsided. In support of this position they quote low mortality figures and cite the dangers attending emergency operation. This attitude has been generally held by the surgeons at the Lenox Hill Hospital.

In this series of cases a comparison of the results of early and late operation indicates that the late operations have been attended by lower mortality, complication, and cholecystostomy rates. However, late operation is less of a risk only if preliminary medical treatment is successful in causing abatement of clinical signs.

When preliminary medical treatment succeeds in producing clinical remission of symptoms, the best results are obtained. The mortality rate is the lowest in the series (2.6 per cent); the complication rate is 9 per cent, and the cholecystostomy rate is 2.1 per cent. The chances of succeeding in producing clinical remission are greater than the chances of failing except when gangrene or perforation of the gall bladder exist.

Results are not as good if preliminary medical treatment fails to cause abatement of clinical signs. In this series 15.2 per cent of the patients failed to respond to medical treatment and these represent our medical failure group. In this group the mortality rate was 5.1 per cent and the complication rate was 15.5 per cent. The cholecystostomy rate was 24 per cent. The high incidence of cholecystomy is an indication of the serious general condition of the patient or the technical difficulties of cholecystectomy under the conditions of medical failure.

It would be desirable at the initiation of treatment to be able to identify those patients in whom the acute cholecystitis will not respond favorably to medical treatment. Correlation of the various clinical and laboratory findings reveals that the most unfavorable factors are patients over the age of 50, the presence of a right upper quadrant abdominal mass and rigidity, jaundice, and a white blood count over 15,000. Singly and particularly in combination these factors increase the chances of medical failure (Fig. 1).

It was also noted that the complications of acute cholecystitis have a considerable influence upon whether or not a patient will respond favorably to medical treatment. A stone in the common duct, perforation, or gangrene of the gall bladder all jeopardize the response to medical treatment (Fig. 2).

The factors influencing the choice of early or late operation would appear from this series to be primarily the age of the patient and the clinical severity

of the disease. The older more seriously ill patients have the greatest chance of failing to respond to medical therapy. We feel that this group is best managed by early operation after adequate medical work-up. In the younger less seriously ill patients, medical treatment will in most instances result in a satisfactory clinical response, and operation may be delayed with benefit to the patient.

SUMMARY AND CONCLUSIONS

1. Three hundred and eighty-one cases of acute cholecystitis were reviewed and of these 318 were treated by operation.

2. There were 16 deaths with an over-all mortality of 4.2 per cent.

3. The series was analyzed with particular reference to failure to respond to medical treatment.

4. When medical treatment succeeded in producing clinical remission, the mortality, complication, and cholecystostomy rate was the lowest in the series.

5. It was found that in this series the patients who failed to respond to medical treatment had a higher mortality, complication rate, and cholecystostomy rate than those who responded favorably to preliminary medical treatment.

6. Fifteen per cent of all patients failed to respond to medical treatment. In this group the disease was more advanced as indicated by history, physical findings, laboratory examinations, and pathologic findings.

7. We feel that early operation should be reserved for the older patients with advanced acute cholecystitis after adequate medical work-up. The patients with less severe forms of acute cholecystitis can best be served by medical treatment and delayed operation.

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EXPERIENCE WITH INTRAVENOUS CHOLECYSTOGRAPHY IN INFANTS AND CHILDREN

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INTRODUCTION

THE intravenous cholecystogram was introduced by Graham and Cole[4] in 1924 and abandoned when the effectiveness of oral studies was recognized. The procedure was revived in 1952 by Frommhold[3] using a compound with less antigenicity, which was sodium iodipamide. The principal contribution of this procedure has been its effective demonstration of the hepatic, cystic, and common bile ducts, either in the presence or in the absence of the gall bladder. At first it was widely used in Europe[2, 6] and later in the United States.[1, 8, 10, 11]

These reports have not included pediatric cases. In 1955 Reichelderfer and Van Hartesveldt[9] described the use of this compound in infants and children who did not have diseases or abnormalities of the biliary system. In the present series, a total of 15 intravenous studies have been performed on 7 infants and 6 children with known or suspected malformations of the biliary tract, at the Childrens Hospital of Los Angeles.†

CLINICAL EXPERIENCE

Intravenous contrast media‡ was used to assist in the identification of an upper abdominal mass in 2 children. The first of these was a 6-year-old girl who had been asymptomatic and without jaundice. A spherical mass was palpable in the right subhepatic space. An intravenous study clearly outlined the size, shape, and position of this structure and demonstrated as well that it had no direct connection with the extrahepatic biliary system (Fig. 1). It was postulated that this was a benign tumor of the liver, a fact which was confirmed by surgical exploration. A second child, 10 years of age, was admitted to the hospital because of abdominal distention without jaundice. Physical examination revealed a large, tender, predominantly right-sided abdominal mass. An exploration disclosed a congenital bile duct cyst and internal drainage was established. Postoperative serial intravenous contrast studies demonstrated its decreasing size as well as its shape and biliary connections (Fig. 2).

The technical procedure in these cases consisted of the slow intravenous injection of 0.6 c.c. of 20 per cent sodium iodipamide solution per kilogram of

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†One case shown in Fig. 2 was treated at Harbor General Hospital, Los Angeles.

‡Cholografin (Squibb).

body weight. The hepatic tumor was outlined in films taken at 20 and 30 minutes following the injection, and the bile-duct cyst was best demonstrated in films taken 30 minutes and 2 hours after the injection.

A similar technique was then employed in 4 patients with known biliary atresia. These infants had been subjected to laparotomy prior to their sixth

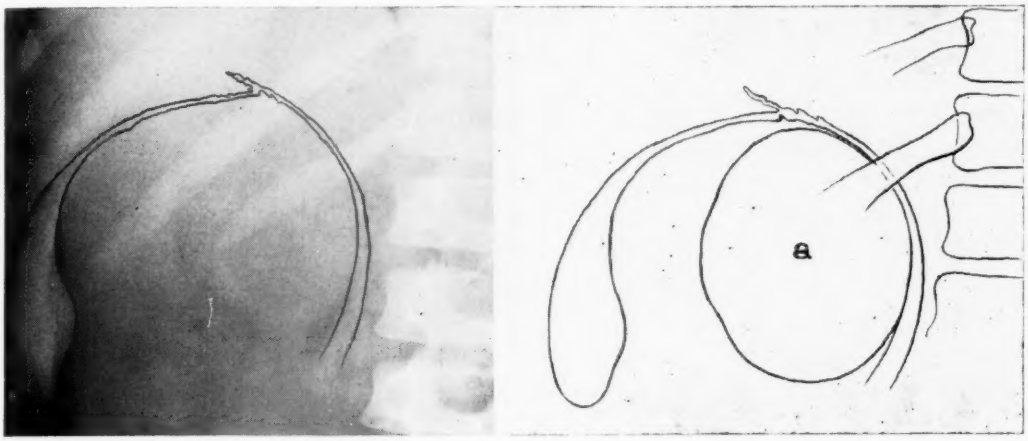

Fig. 1.—Benign hepatic tumor in a 6-year-old girl, outlined by study with intravenous sodium iodipamide (Cholografin). Serial films identified all portions of the extrahepatic biliary system and clearly delineated the tumor (*a*).

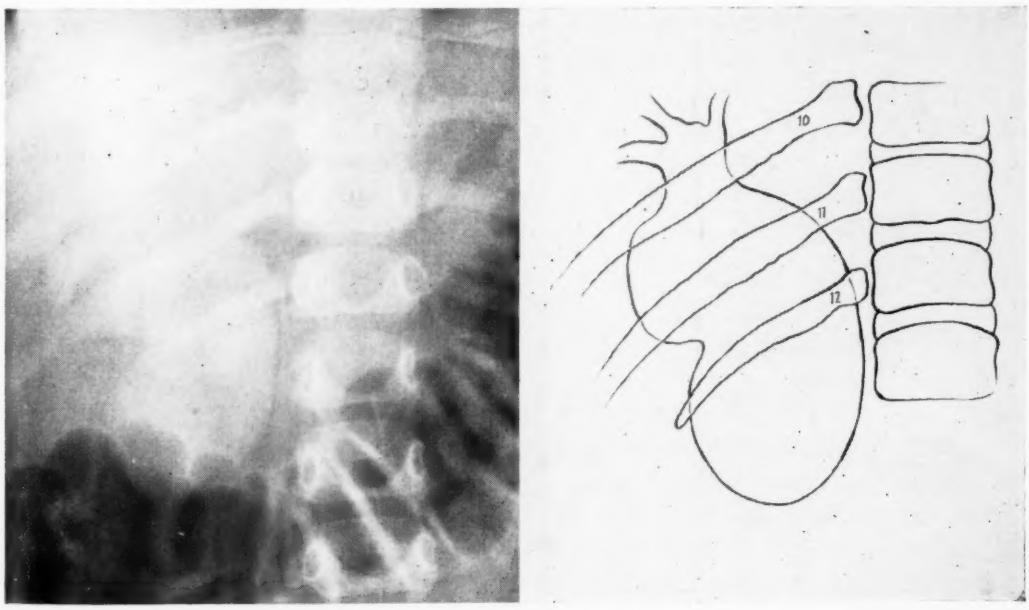

Fig. 2.—A congenital bile-duct cyst demonstrated in a 10-year-old girl with intravenous sodium iodipamide (Cholografin). Serial studies have shown progressive diminution in size following internal drainage.

month of life. At the time of the intravenous study these children were 7 months, 2 years, 2½ years, and 5 years of age. Between 1 and 1.2 c.c. of sodium iodipamide per kilogram of body weight, which is 3 to 4 times the adult dosage,

was administered and exposures were made during a 4-hour observation. A repeat study, using 1.6 c.c. per kilogram of body weight, approximately 5 times the adult dosage, was performed in 2 cases. No visualization of the biliary tract was obtained in any of these patients.

Intravenous studies were then performed on 3 patients who had initially been regarded as having biliary atresia or stenosis and were explored surgically in early infancy. The patency of the extrahepatic and major intrahepatic radicles had been demonstrated in each instance by operative cholangiography. All of these children had hepatomegaly, and alterations in liver function were demonstrated by multiple tests at one stage of their illness. Two had several attacks of mild jaundice prior to the intravenous study, at the age of 9 years, 2 years, and 18 months, respectively. None were clinically jaundiced at the time of the procedure. The diagnoses in these cases were xanthoma tuberosum multiplex with biliary cirrhosis for the first case; biliary cirrhosis, probably secondary to intrahepatic biliary atresia not in the major radicles, for the second infant; and neonatal hepatitis with possible posthepatic cirrhosis in the third case. An injection of 1.2 c.c. per kilogram of body weight was used in each instance. Visualization of the extrahepatic biliary tract was accomplished only in the third case of neonatal hepatitis.

Four studies were performed on infants, from 6 weeks to 2 months of age, who presented problems in the differential diagnosis of protracted neonatal jaundice. The biliary tree could not be visualized despite the use of 1.6 c.c. of dye per kilogram of body weight. Surgery revealed an extrahepatic biliary atresia in 3 of these and an apparent intrahepatic atresia in the fourth.

In all of these 15 patients an intradermal injection of 0.1 c.c. followed 10 minutes later by intravenous injection of 0.25 c.c. of 20 per cent sodium iodipamide was carried out prior to the major injection. There were no positive reactions. Following administration of the total dosage of this compound, there were no major untoward reactions, although nausea and vomiting were noted in 2 children.

DISCUSSION

The study of 2 children with upper abdominal masses demonstrated the apparent effectiveness of this compound in delineating the extrahepatic biliary tree and its saeculations when they are present. The size of the choledochal dilatation, which was 15 cm. in diameter, did not produce a dilution sufficient to prevent its repeated opacification by sodium iodipamide. Patients with known biliary atresia were studied with a similar technique, employing massive dosage. It is now assumed that liver function is altered to such a degree by obstructive biliary cirrhosis in these patients that the dye is excreted entirely by the renal route.

In children with a patent extrahepatic biliary system but with evidence of chronic hepatic disease, demonstration of the ducts is usually not possible despite the use of dye concentration between 2 and 5 times that ordinarily used for adults. None of these patients were clinically jaundiced at the time of the study. The degree of hepatic insufficiency is apparently the determining factor

in visualization of the extrahepatic tract. Diagnostic use of this method in patients with prolonged jaundice following birth was made in 4 cases. No visualization could be obtained and an exploratory operation revealed biliary atresia. The converse, that is, the ability of the intravenous cholecystogram to demonstrate the extrahepatic tree in neonatal hepatitis, would be of greater significance. In the only case pertinent to this point, the patient was convalescent at the time of the effective visualization of the biliary tract.

SUMMARY

Intravenous cholecystography, employing 20 per cent sodium iodipamide (Cholografin) has been employed in 15 studies in infants and children with suspected anomalies of the extrahepatic biliary system. A bile-duct choledochal cyst can be differentiated from other possible abdominal masses by this technique. In infants with biliary atresia no visualization of the intrahepatic radicles was possible. In infants in whom a patent extrahepatic system had been demonstrated but who had severe hepatic damage without jaundice, visualization was usually not obtained. In the recovery phase of one case of neonatal hepatitis, the biliary tract was demonstrated.

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NEEDLE ASPIRATION OF THE GALL BLADDER AT THE TIME OF LAPAROTOMY TO DETERMINE THE PRESENCE OR ABSENCE OF CALCULI

A Diagnostic Aid

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PATIENTS having elective surgery have usually been in the fasting state since the evening meal of the preceding day. The gall bladder has had no reason to empty itself nor the sphincter of Oddi to relax. For this reason many times when the abdomen is opened the gall bladder will be found to be full, distended, and tense. Its walls are not easily collapsed nor is the organ readily emptied by palpable pressure. Because of this, examination of its contents is inadequate. Small stones and occasionally calculi of considerable size may be overlooked.

Needle aspiration of the gall bladder is a simple and very effective means of obviating the above difficulty. The technique is quite simple. A No. 18 gauge needle fitted to a large syringe is all that is required. We have used a 20 c.c. syringe for ease of handling. A warm saline pack is placed beneath the gall bladder and either the surgeon or the assistant elevates the gall bladder into the wound and the other aspirates its liquid contents through the fundus. Usually after approximately 30 to 40 c.c. of bile are removed, the organ is sufficiently collapsed to afford excellent palpation. The puncture wound made by the needle is closed and inverted with 3-0 intestinal catgut suture; care is taken not to enter the gall bladder lumen. Drainage is unnecessary unless further biliary surgery is done.

Obviously this procedure is not necessary when elective cholecystectomy is being done for cholelithiasis previously diagnosed by cholecystography. We feel it is quite useful in routine examination of the gall bladder, when laparotomy is being done for some other disease in the upper abdomen and when the examination is inadequate by the usual technique, or when exploratory laparotomy is resorted to for persistent symptoms after repeated cholecystography is negative. During the past 5 years, we have performed this procedure in approximately 50 instances. Conservatively, we feel that abnormalities that would otherwise have been missed have been noted in 10 per cent of the cases.

Perhaps many surgeons are now utilizing this diagnostic aid in gall-bladder surgery. However, we have not seen it alluded to in the literature. We report this procedure because of its simplicity, and because we have on many occasions been very agreeably surprised with its yield.

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PREPARATION AND BIOASSAY OF A LOW MAGNESIUM LIQUID DIET FOR HUMAN CONSUMPTION

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THE metabolic role of magnesium has been studied previously in clinical and animal experimentation, but the investigation of the biologic importance of magnesium has been hampered by difficulties in obtaining a low magnesium diet of sufficient palatability to permit clinical studies. It is reasonable to suppose that a low magnesium intake is as essential in magnesium balance studies as a low calcium intake has been shown to be in the interpretation of calcium studies.[1] Current food tables[2, 22, 29] record the ubiquitous distribution of magnesium in virtually all common food substances and indicate the impossibility of obtaining a palatable or nourishing low magnesium diet. A diet acceptable only to rodents has been achieved by combining washed casein, sucrose, vegetable oils, fish oils, and a salt mixture.[4, 21] In these diets the magnesium content was reduced to approximately one part per million by weight, and animal experimentation frequently has taken advantage of the growth in immature animals to facilitate the production of a relative magnesium deficiency. Another technique for decreasing the absorption of magnesium is the introduction of Permutit, a cation exchange resin, into the diet. A content of approximately 10 per cent Permutit Z produces a negative magnesium balance in rats,[14] but a disadvantage of this method is the depletion of other ions because of the nonspecific binding by the cation exchange resin in the gastrointestinal tract. Although this may be largely compensated for by providing additional amounts of cations other than magnesium, such use of a resin would prove to be a troublesome method in humans where the bulk of the resin and its taste are commonly associated with nausea, vomiting, diarrhea, constipation, or crampy abdominal pain. Another means of achieving a low magnesium absorption is the addition of sodium phytate to the diet.[15] Sodium phytate forms an insoluble and unabsorbable complex with calcium and magnesium and decreases the absorption of both of these cations. However, this agent has the disadvantage of binding both bivalent cations in the gastrointestinal tract, and its extended use is usually associated with unpleasant gastrointestinal symptoms.

Since 1949 a number of reports have presented methods for the reduction of cations in milk by ion exchange resins.[3, 8, 9, 12, 13, 23] This treatment was developed to improve the stability of milk products and to facilitate the reconstitution of powdered dairy products to homogeneous liquids. Substantial

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amounts of calcium and magnesium have been removed from milk by this technique, but no deliberate attempt to remove virtually all of the magnesium has been brought to our attention. In view of the difficulties in obtaining a low magnesium diet and in view of the reports suggesting the effectiveness of exchange resins in binding electrolytes in milk, a method of treating milk products to obtain a food suitable for human consumption and low in magnesium has been developed. The principles involved in the selective removal of electrolytes from complex solutions of ions have been discussed elsewhere.[16, 19, 24]

METHODS

Dairy Product.—In addition to whole milk a commercial powdered milk product known as Pream* was processed to remove magnesium. Pream appeared particularly suitable in that the commercial preparation utilizes a cation exchange resin to reduce the calcium content giving to the product the features of rapid reconstitution to a homogeneous liquid from the dry powder and of preservation of the milk proteins largely unaltered from their native state. The protein, carbohydrate, fat, moisture, and caloric content of Pream powder is as follows[25]: protein, 8.0 to 8.4 per cent; lactose, 61.5 to 62.0 per cent; butterfat, 27.0 to 27.4 per cent; moisture, 1.5 to 1.8 per cent; calories, 5.2 per gram.

The Pream powder has been stored in metal or glass containers at room temperature until processing. It is then reconstituted by making 225 Gm. of powder up to a volume of 1 liter with tap water. The Pream so reconstituted has an approximate protein content of 1.8 per cent, a lactose content of 14 per cent, a butterfat content of 6.1 per cent, and contains approximately 1.2 calories per cubic centimeter. The relatively low protein and high caloric values of this reconstitution are noteworthy in contrast to whole milk.[28] Reconstitution of the Pream with less water results in a greater viscosity and loss of homogeneity with consequent problems in achieving a smooth flow in a resin exchange column.

Ion Exchange Resin.—The resin employed has been a cation exchange resin of the styrene sulfonic acid type with a high porosity. The resin should be supplied in the hydrogen form inasmuch as bacterial growth during transportation within the resin is minimized by a low pH. The total capacity of the resin should approximate 5.0 ± 0.3 meq. per dry gram, and a 20 to 50 mesh size is convenient in processing milk. The resin† is commonly supplied with an approximate moisture content of 70 per cent by weight and is kept moist until it is used in the processing of the milk products.

Preparation of the resin: To prepare 4 resin columns for the processing of whole milk or Pream the following procedure has been found satisfactory. The moist resin (2,200 c.c.) is measured out and transferred to a large Buechner funnel. The type of funnel standing free on a table top is convenient and is available with the large capacity to facilitate the subsequent washes. Two No. 1

*A patented dairy product processed by the M & R Dietetic Laboratories, Inc., Columbus, Ohio.

†A satisfactory resin designated as Dowex 50-X4 is obtainable from the Dow Chemical Company, Midland, Mich.

Wattman filter papers are placed in the Buechner funnel prior to the transfer of the resin, and the following washes are accomplished in rapid succession without allowing the resin to dry: 4.5 L. saturated NaCl solution (approximately 6 M NaCl), 1.5 L. 0.06 M KOH and 0.04 M NaOH solution, 4.5 L. demineralized H_2O, 1.5 L. 0.05 M Na_2HPO_4 solution, and 1.5 L. 0.03 M KCl and 0.02 M NaCl solution.

The initial wash is to remove the aqueous solution sequestered in the large macromolecular pockets within the resin compound. From these interstices a colored aqueous solution may leach out, and to remove this "color throw" large volumes of fluid are required. The compounds causing the discoloration are not toxic, nor do they modify the taste of the processed dairy product. However, their removal is desirable to avoid a yellowish discoloration of the milk product. The potassium hydroxide and sodium hydroxide solution is the regenerating alkali converting the resin to the potassium and sodium cycle preparatory to the exchange binding of magnesium and calcium. After removal of the excess alkali with water the pH is adjusted toward a more physiologic value with the dibasic sodium phosphate solution. The final wash with potassium and sodium chloride is to remove the excess phosphate buffer, achieve an ion concentration approximately that of milk, and to saturate the resin with potassium and sodium in amounts corresponding to their ionic ratio of approximately 3 to 2 in milk.[29]

Contact time: To standardize the processing it is necessary to evaluate the duration of the contact of the dairy product with the resin compound. If a uniform flow is achieved, the contact time will be proportional to the volume of the resin as well as the rate of flow through the column. Contact time measured in minutes is defined as the volume of moist resin in cubic centimeters divided by the flow of the solution being processed in cubic centimeters per minute. If varying amounts of resin are used and the procedure is modified from the description given here, particular attention should be directed to establishing a rate of flow producing a contact time equal to or larger than the time recommended. In view of the difficulty in arranging an absolutely uniform rate of flow through a resin column, the quantity of resin in relation to the amount of solution processed is in excess so that the rate of flow and contact time are not critical features of the method. A contact time of 5 minutes or greater is recommended, and this is achieved by each column containing 550 c.c. of resin and by limiting the rate of flow to less than 110 c.c. per minute.

Apparatus: The resin column is arranged so that milk may be fed into the column by gravity through a flexible piece of rubber tubing which will permit the control of the flow by means of a pinch cock. The resin is supported in a glass tube approximately 3.5 cm. in diameter and 60 cm. in length by means of two layers of 100 mesh nylon bolting cloth which are secured in position just above the lower end of the column with a rubber stopper with multiple holes. The collecting vessel should have a side arm to permit the application of steady suction, if necessary to obtain the desired rate of flow. Into each column is measured 550 c.c. of resin from the Buechner funnel after the last wash. In

transferring the prepared resin to the column, it is important to add resin and 0.03 M KCl and 0.02 M NaCl solution together so that the resin is always submerged in saline. All air will then be removed from the resin as it settles, and trapped air causing channeling will be prevented. As the dairy product is processed, the initial 200 c.c. or so will be almost pure salt solution. This is discarded, and after the salt solution has been displaced from the column, the dairy product is collected in a fresh container.

Regeneration of the resin compound: After each column has processed 3.5 L. of milk, the resin is treated as follows. To remove any residual milk, 0.5 L. of 0.03 M KCl and 0.02 M NaCl solution are run through each column, and then the resin from 2 columns is combined in one large bottle. Two liters of 0.5 M H_2SO_4 are added, and the suspension of resin and acid are shaken frequently over a period of 2 hours. The resin is then allowed to settle, and the supernatant is discarded. The wash is repeated once again, and the resin is allowed to stay overnight with a third washing of 2 M H_2SO_4. If the resin is not to be used at once, it may be left submerged in the sulfuric acid for an indefinite period until it is necessary to prepare the resin for another extraction of magnesium from milk or Pream by the steps outlined under preparation of the resin.

Addition of salt mix: On the basis of previous studies concerning the optimal salt content of experimental rat diets[17] a salt mix was prepared, suspended in a few cubic centimeters of distilled water, and added to the processed dairy product to provide traces of metals presumably effectively removed or reduced in amount by the cation exchange resin. Each liter of the processed dairy product had the following amounts of minerals added to the salt mix: iron, 23.0 mg.; manganese, 5.6 mg.; iodine, 2.6 mg.; zinc, 0.5 mg.; copper, 0.5 mg.; and cobalt, 0.02 mg. To compensate for the reduction of calcium caused by the resin 1.88 Gm. of $CaCl_2$ were added as 4 M $CaCl_2$ solution per liter. Care must be taken to avoid too rapid an addition without gradual mixing as troublesome formation of large curds may occasionally take place. The sodium, potassium, and magnesium content are considered in the next section, and the low potassium content of the processed Pream has been altered by adding from 20 to 60 meq. of potassium as 1.75 M K_2HPO_4 depending on the demands of the particular study.

CHEMICAL ANALYSIS

In Table I data are presented on the composition of the reconstituted Pream and on the composition of the processed dairy product. The analytical methods for nitrogen,[6] sodium,[31] and potassium[31] require no comment, and the magnesium was determined by a colorimetric method coupling the magnesium ion with titan yellow dye as reported by Garner.[7] The limitations of this technique as noted in other reports[10, 20] are not without interest in the application of the titan yellow method to the determination of magnesium in the presence of calcium, phosphorus, and other possible interfering substances. As anticipated the nitrogen content remains essentially unaltered by the resin with the slight

decrease noted due to the almost insignificant dilution caused by the admixture of the dairy product and the solutions used to prepare the resin column. The increase in the sodium content of approximately 11 meq. is balanced by a 2 meq. decrease in the potassium content, by a 2 meq. decrease in the magnesium content, and presumably by a decrease in calcium and other divalent ions in the effluent for which no analysis was made in this study.

TABLE I. NITROGEN, SODIUM, POTASSIUM, AND MAGNESIUM CONTENT OF PREAM

	NITROGEN (GM./L.)	SODIUM (MEQ./L.)	POTASSIUM (MEQ./L.)	MAGNESIUM (MEQ./L.)
Unprocessed Pream (225 Gm./L.)	3.02	63.1	5.22	1.91
S.E.	0.007	0.16	0.01	0.037
Number of analyses	18	16	16	15
Processed Pream (225 Gm./L.)	2.98	74.1	3.3	Less than 0.12
S.E.	0.026	0.20	0.18	
Number of analyses	30	16	16	33

S.E. = standard error of the mean values tabulated.

In view of the unfavorable analytical situation in the effluent for the determination of traces of magnesium, the results of our colorimetric analyses were checked by two independent laboratories employing two different techniques. By flame spectrophotometry* only trace amounts of magnesium were possibly identified, and these amounts may have been a manifestation of the background illumination from the sodium present in the sample. By more classical techniques employing ammonium phosphate precipitation,[27] magnesium was found to be present in the order of 1 part per million or approximately 0.08 meq. per L. of the processed dairy product. The precise value of the magnesium content remains unknown, and we have accepted our more conservative estimate of 0.12 meq. per L. as the highest limit. In all probability the magnesium content is a great deal less. Confirmation of the efficiency of the resin column in reducing the magnesium content of the Pream was obtained in studies employing Mg^{28}, a radioactive isotope. Over a 500-fold decrease in the magnesium content was demonstrated by this direct technique.

BIOASSAY

To determine the efficacy of this diet in establishing a magnesium deficit, 6 weanling rats and 12 adult rats of the Hisaw strain were placed on the processed Pream diet. The diet employed had the composition stated above and had a total of 23 meq. potassium per liter. The weanling rats on the same diet were caged together, and the adult rats were kept in adjacent, identical, individual, metabolic cages to permit collection of their urine and stool as part of another study related to magnesium metabolism. The liquid diets in all instances were supplied in excess of the demands made by the animals.

The 6 weanling rats were part of a litter separated from their mother at about one month of age. These 6 rats were all females of the litter and were

*These analyses were performed through the courtesy of Dr. Marvin Margoshes, Peter Bent Brigham Hospital.[26]

divided randomly into 2 groups of 3 rats apiece. The 2 groups were caged adjacently, and the liquid diet provided was identical except that 11.5 meq. of magnesium as 1 M $MgSO_4$ were added per liter to the diet of one group. Both groups of rats were given a vitamin supplement in fish oil 3 times a week by allowing them to lick a medicine dropper filled with the preparation. Table II records the changes in weight of the 2 groups of weanling rats. The rate of growth is substandard for those rats on the magnesium enriched diet according to one authority,[5] and we believe the liquid character of the diet and its relatively low protein content are responsible for the substandard growth. The loss of weight in those animals placed on a magnesium free diet was particularly striking in contrast to those that gained on the same diet with added magnesium. The wasting course of the deficient rats was accompanied by a loss of gloss in their coat, by a sparseness of body hair with patches of absent hair, by a blotchy erythema of the anterior portion of the head extending over the nose, by a similar dermatitis extending over the tail, and by the appearance of scabs and scales over the areas of dermatitis where the skin apparently was weeping a protein rich fluid. At times crusting and exudate about the nostrils and eyes were prominent in the magnesium deficient group, and all of these changes were absent in the weanlings given the supplement of magnesium. Fig. 1 gives some concept of the differences between the 2 groups in regard to size and condition of the integument at the conclusion of a 2-month period on the special diets. These findings are in harmony with previous reports concerning magnesium deficiency in rats.[11, 18, 21]

TABLE II. WEIGHT CHANGES IN WEANLING RATS

	WEIGHT IN GRAMS (AGED 1 MONTH)	WEIGHT IN GRAMS (AGED 3 MONTHS)
Processed Pream (225 Gm./L.); less than 0.12 meq. of Mg per liter	130	109
	144	134
	155	137
Mean	143	127*
Processed Pream (225 Gm./L.); 11.5 meq. of Mg added per liter	145	149
	149	158
	150	170
Mean	148	159*

*A test of significance of the 32 Gm. difference in these means by t test indicates $0.02 < P < 0.05$.

The 12 adult rats were derived from 2 litters with those of the same sex originating from the same litter. The rats were assigned randomly to separate metabolic cages and kept together as a unit on a large rack. They were divided into 3 groups of 4 rats apiece, and 2 groups received only the liquid diet with or without added magnesium. The liquid diets were the same as those provided the weanling rats, including the vitamin supplement, and the third group of 4 rats was placed on the routine laboratory fare* with water as desired. Table III records the changes in weight in the adult rats as influenced by these dietary routines. The male rats were heavier and more obese than the female rats and lost more weight in the study, presumably a reflection of their larger deposits

*Purina Laboratory Chow manufactured by Ralston Purina Co., St. Louis 2, Mo.

TABLE III. WEIGHT CHANGE IN ADULT RATS

	SEX	WEIGHT IN GRAMS (AGED 3 MONTHS)	WEIGHT IN GRAMS (AGED 6 MONTHS)	DIFFERENCE M	DIFFERENCE F
Processed Pream (225 Gm./L.); less than 0.12 meq. of Mg per L.	M	355	268	−87	
	F	259	219		−40
	M	338	275	−63	
	F	253	217		−36
Mean				−75	−38
Processed Pream (225 Gm./L.); 11.5 meq. of Mg added per L.	M	357	306	−51	
	F	250	248		−2
	M	342	268	−74	
	F	211	215		+4
Mean				−63	+1
Regular laboratory diet	F	379	365	−14	
	M	242	251		+9
	F	405	319	−86	
	M	249	284		+35
Mean				−50	+22

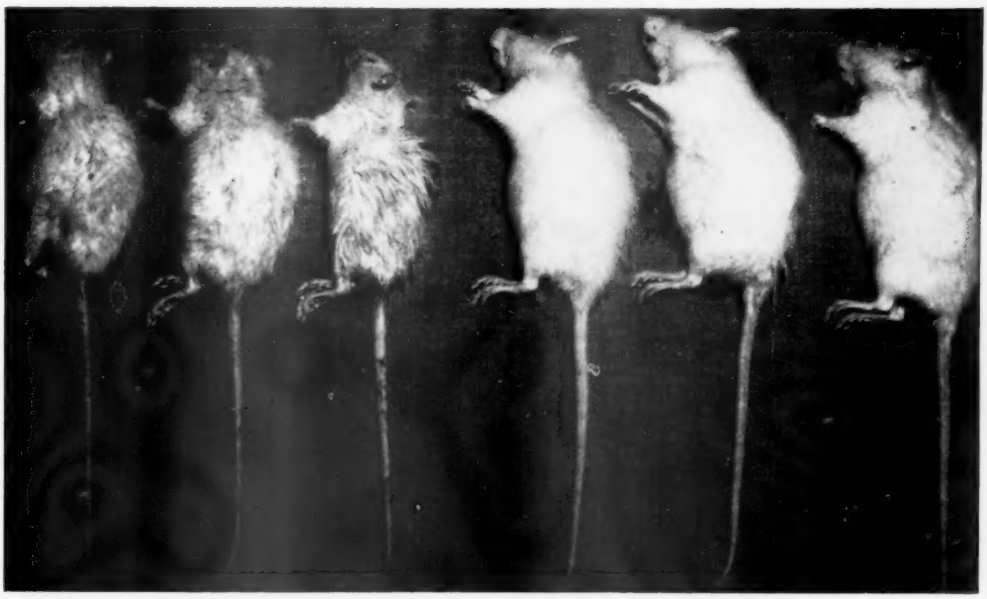

Fig. 1.—A comparison of the appearance of the magnesium deficient rats on the left with those on the right given the same diet and a magnesium supplement.

of fat. The 3 routines permit a comparison of the influence on weight of caging the rats in exposed metabolic cages while on a regular diet, while on a liquid diet, and while on the same liquid diet devoid of magnesium. A test of significance is presented in Table IV where the analysis of variance and the F test comprise the statistical argument for the effect of the diets on the weight of rats of the same sex. That the effects in the adult rats are not more decisive is in part due to the general loss of weight in the male rats, evidently a consequence of the unfavorable environment provided by a small and exposed metabolic cage

lacking any natural seclusion. The marked influence of such environmental factors has been stressed before.[5] It is also in part due to the well-known difficulty in producing a pronounced magnesium deficiency syndrome in adult rats where the reserves of magnesium in the skeleton may contribute to the demands of the animals and where the cessation of rapid growth no longer allows the effects of a dietary deficiency to be compounded by the requirements for an increase in body mass.

TABLE IV. ANALYSIS OF VARIANCE OF THE PREAM DIETS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE
Diet	1	1,326	1,326
Sex same diet	2	5,402	2,703
Rats same sex and diet	4	578	145
Total	7	7,306	

Test of significance of effect of diets[30]: $F = \frac{1,326}{145} = 9.14$; $0.01<P<0.05$.

SUMMARY

The need for a diet virtually free of magnesium and suitable for human consumption has been fulfilled by preparing a basic liquid diet derived from milk products and by processing it with a cation exchange resin. The composition of the product may be adjusted by the addition of various mineral components, and chemical analyses reveal a magnesium content of less than 0.12 meq. per liter or approximately 1 part per million of magnesium by weight. Biologic confirmation of the specific deficiency is presented in the growth of weanling rats and in the loss of weight in adult rats. The metabolic studies of human subjects on this diet will be considered in subsequent reports.

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THE ACID SECRETORY RESPONSE TO HISTAMINE AND INSULIN HYPOGLYCEMIA AFTER VARIOUS OPERATIONS ON THE STOMACH

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DURING the performance of pre- and postoperative acid secretory tests on duodenal ulcer patients, it has been noted that after some operations the effect of histamine has been altered so that subcutaneous administration of this drug results in a diminution of the volume of gastric juice below control (basal) values while the concentration of acid rises slightly or remains unchanged. A similar effect results from stimulation by hypoglycemia induced by insulin given intravenously. It is the purpose of this report to present these data and discuss their surgical and physiologic significance.

METHODS AND MATERIAL

The preparation of the patients, collection of samples, and methods of analysis have been described in earlier publications.[11, 12] The patients all had active duodenal ulceration at the time the preoperative studies were carried out. All the postoperative patients were relieved of their ulcer difficulties, except for the group with marginal ulcers after partial gastrectomy included in Table I. Histamine diphosphate, 0.5 mg., was administered subcutaneously in that particular test. Hypoglycemia was induced by the intravenous administration of either 12 or 15 units of insulin (Ciba) depending upon the dietary intake of the patient prior to the test. Blood sugar concentration was lowered to at least 50 mg. per 100 ml. in every instance.

In addition to the preoperative patients with duodenal ulcer (intact stomach), the following groups of postoperative patients have been studied: (1) 6 patients that had sleeve resections of the mid-portion of the stomach with exclusion of the antrum and gastrojejunostomy (first-stage gastrectomy);[8] (2) 8 patients that had standard ⅔ to ¾ distal subtotal gastrectomy with gastrojejunostomy; and (3) 50 patients that had antrum exclusion, vagotomy, and gastrojejunostomy. In these patients the stomach was transected in its mid-portion, the distal end closed, and a gastrojejunostomy performed. There was a large proximal (50 per cent) pouch. In addition to these patients, the data published by Farmer and co-workers[5] on 10 patients with vagotomy and gastroenterostomy, 18 patients with 50 per cent distal

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TABLE I. VOLUME, AVERAGE pH, AND MILLIEQUIVALENTS OF FREE ACID PER HOUR DURING BASAL PERIOD AND AFTER STIMULATION WITH HISTAMINE AND INSULIN HYPOGLYCEMIA

ANATOMIC ARRANGEMENT	NO. OF PATIENTS	BASAL			HISTAMINE			INSULIN		
		VOLUME ML./HR.	AVERAGE pH	MEQ. FREE ACID/HR.	VOL. ML./HR.	AVERAGE pH	MEQ. FREE ACID/HR.	VOLUME ML./HR.	AVERAGE pH	MEQ. FREE ACID/HR.
Intact stomach	75	97	1.8	4.4	175	1.2	16.0	129	1.3	10.5
Antral exclusion (1st stage gastrectomy)	6	74	3.3	1.3	118	2.0	6.4	81	2.0	3.3
Antral exclusion with vagotomy	50	81	4.9	0.7	79	4.1	0.9	38	4.5	0.7
Hemigastrectomy with vagotomy*	18	79	5.8	0.1	55	4.7	0.9	56	5.6	0.2
Posterior gastroenterostomy with vagotomy*	10	109	4.5	2.6	163	2.7	8.8	51	3.7	1.1
Partial gastrectomy (⅔-¾)†	8	89	5.8	0.3	65	4.8	1.3	41	5.0	0.6
Partial gastrectomy with recurrent ulceration*	5	115	2.8	3.6	182	2.4	10.6	135	1.8	5.7

*Data from Farmer and co-workers.[5]
†Data on 6 of these patients from Farmer and co-workers.[5]

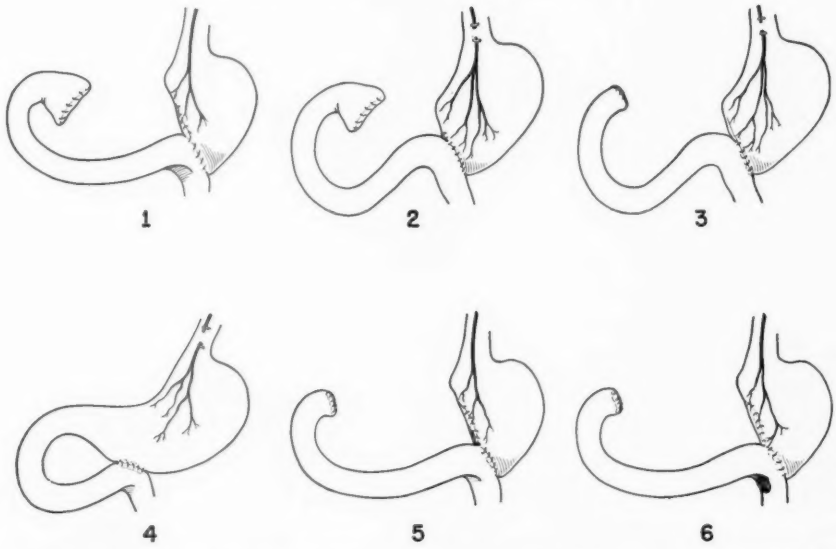

Fig. 1.—Diagrammatic representation of the anatomic result after the various operations under consideration. (1) Antral exclusion (first-stage gastrectomy), (2) antral exclusion with vagotomy (50 per cent proximal pouch), (3) hemigastrectomy with vagotomy (50 per cent proximal pouch), (4) posterior gastroenterostomy with vagotomy, (5) partial gastrectomy (⅔ to ¾ distal resection), and (6) partial gastrectomy with jejunal ulcer.

gastrectomy with vagotomy, and 5 patients with marginal ulceration after partial gastrectomy are included. The data from these additional patients as well as the results from other groups of patients studied by Smithwick and Kneisel[10] are directly comparable since identical methods were used, except that 0.4 mg. of histamine was used in their testing instead of 0.5 mg. The anatomic results of the different operative procedures under discussion are shown in Fig. 1.

RESULTS AND DISCUSSION

In Table I the acid secretory data in response to histamine and insulin hypoglycemia after various operations on the stomach are presented. Also included are a group of preoperative duodenal ulcer patients and another group of patients that had recurrent ulceration at the gastroenterostomy after partial gastrectomy. It can be seen that the patients with intact stomachs responded to both histamine and insulin stimulation by increasing the volume and acidity. This is the usual result of stimulation of this sort in both duodenal ulcer patients and normal individuals although the amount of acid produced by the latter is appreciably less than observed in patients with duodenal ulcer.

The antral exclusion (first-stage gastrectomy) patients had a sleeve of the mid-portion of the stomach resected as well as a variable portion of the antrum. The proximal remnant was $\frac{1}{3}$ to $\frac{1}{4}$ of the stomach. The transection line was at the same point as in partial (subtotal) gastrectomy. These patients secreted less acid than did those with intact stomachs under basal conditions and after stimulation. Both volume and acidity were increased over basal levels after stimulation by histamine and insulin hypoglycemia. On the other hand after subtotal gastrectomy in which the distal $\frac{2}{3}$ to $\frac{3}{4}$ of the stomach was removed, stimulation by histamine and insulin produced decreases in volume by approximately 50 per cent and only small increases in acid concentration.

In a previous communication evidence such as this was considered in an attempt to more clearly establish the function of the gastric antrum.[12] It was suggested that the most plausible explanation was that the antrum was a source of afferent impulses which influenced central reflex centers to contribute to the general tonic state of those centers and their response to stimulation. It is believed that the final effect of such reflex activity is acetylcholine liberation at the gastric secretory units.

In Table I the data from three groups of vagotomized patients are shown. The vagotomy–posterior gastroenterostomy and the vagotomy-hemigastrectomy data were taken from the report of Farmer, Howe, Porell, and Smithwick.[5] The significant observation from this comparison is that vagotomy with posterior gastroenterostomy does not result in reversal of the volume increase that normally results from histamine in comparison with the preceding basal period. In this group of patients there was an average rise of 40 per cent. On the other hand, when insulin hypoglycemia was used as the means of stimulation there was a 50 per cent decrease in the volume of gastric secretion. The free acid output followed a similar pattern. For example, histamine caused a threefold increase in free acid output while insulin hypoglycemia produced a decrease in the quantity of free acid as compared with the preceding basal period.

In the antrum exclusion–vagotomy group of patients, histamine stimulation did not produce any increase in volume as judged by the average figures. Examination of the individual tests shows that in approximately half of the patients there was a rise in volume, usually small, after histamine and in the

other half there was a fall. It is perhaps significant that with only three exceptions every patient secreting more than 100 ml. per hour during the basal periods responded with a decrease in volume after histamine stimulation. There was a small average increase in acidity after histamine. No free acid appeared in 40 per cent of the patients. During insulin hypoglycemia the volume of secretion was approximately half that of the basal period.

The hemigastrectomy-vagotomy patients of Farmer and associates in general showed the same type of secretory pattern as the patients with antrum exclusion and vagotomy except that the reduction in volume after histamine was greater. The acidity was approximately the same. After insulin there was a reduction in volume as compared with the basal period. Acidity increased only very slightly during insulin stimulation.

What interpretation of these results can be given? Hypoglycemia induced by insulin initiates a complex series of physiologic events directed toward elevation of blood sugar to normal. A major aspect of this reaction to hypoglycemia is stimulation of the sympathoadrenal system.[4] Characteristic of acute sympathetic discharge, the effects are diffuse, partly due to direct nervous effects upon muscles and glands and also due to circulating epinephrine. One might reasonably question why intense parasympathetic stimulation, apparently confined to the cranial outflow, also results from the state of hypoglycemia. Teleologic reasoning suggests that this may represent preparation of digestive environment for rapid breakdown of whole food into a form that can be assimilated for correction of the hypoglycemic condition. The elaboration of acid and enzymes and increased motility in the stomach after insulin stimulation would be consistent with such an interpretation. Similarly increased gastric acidity and parasympathetic activity lead to pancreatic secretion, again a means of alleviating low blood sugar. It is the author's opinion that only from a consideration of the over-all effect of hypoglycemia can a reasonable interpretation of the effects of this form of stimulation on gastric secretion be made.

In earlier presentations it has been shown (1) that one of the effects of gastric antrum excision is to lessen or abolish the result of parasympathetic stimulation by hypoglycemia[12] and (2) that separation of the antrum from the body and fundus of the stomach lessens or, under some conditions, abolishes the acid secretory effect of hypoglycemia.[11] This latter phenomenon is thought to be due to interruption of postganglionic parasympathetic fibers passing from the distal end of the stomach proximally. It is quantitatively important because of the concentration of ganglion cells in the antral area and along the lesser curvature.[2] These facts have an important bearing upon the comparison of the effects of hypoglycemia after such dissimilar operations on the stomach as two-thirds distal gastrectomy and vagotomy with posterior gastroenterostomy. If our interpretation of the effect of gastrectomy is correct, then the final derangement of function after gastrectomy and vagotomy is the same, namely, a reduction in acetylcholine at the neuroeffector junction. If this is the case, the patient in each instance is left with a parietal

cell area with reasonably intact sympathetic innervation and largely deprived of parasympathetic supply. It is believed that here is the explanation of the observed decrease in volume that follows insulin stimulation after operations that have been successful clinically for control of duodenal ulcer. In Table I it can be seen that volume increase in response to insulin stimulation occurred in the ulcer patients with intact stomachs, in the group of patients with antrum exclusion (first-stage gastrectomy[8]), and in those patients in whom partial gastrectomy failed to control the ulcer disease, while in 4 other groups of patients with different operative procedures, all reasonably satisfactory for duodenal ulcer, the result of insulin hypoglycemia was a decrease in volume. Whether unopposed local sympathetic discharge or circulating epinephrine is responsible for the observed effects cannot be stated at present. However, it seems probable that it is the latter since Smithwick and Kneisel[10] studied patients that had both vagotomy and splanchnicectomy, and the reductions in volume after insulin were even more pronounced than in any of the groups of patients shown here. Also we have studied 8 patients whose stomachs were completely denervated except for sympathetic fibers running along with the right gastric and right gastroepiploic vessels (esophagectomy), and they showed the least volume during insulin stimulation of any group studied (average 18 c.c. per hour). It thus appears that interruption of sympathetic innervation to the stomach along with vagotomy causes greater decrease in volume of secretion during hypoglycemia than vagotomy alone. It may be that cholinergic parasympathetic fibers carried in the splanchnic nerves are more important than heretofore recognized[2] and the lessened volume response to insulin hypoglycemia is a reflection of more complete parasympathetic denervation in those instances where both sympathetic and vagus nerves have been sectioned.

Histamine administration causes increased volume and acid concentration of gastric juice in patients with intact stomachs. After some operations this response is modified so that this drug causes a decrease in volume of gastric juice and slight or negligible increases in acid concentration. Antrum exclusion (first-stage gastrectomy) is a notoriously unsuccessful operation for duodenal ulcer, and as one might predict histamine stimulation causes increase in volume and acidity. Excision of the antrum results in reversal of the usual volume response to histamine so that after distal subtotal gastrectomy, histamine stimulation results in a lessening of the volume secreted and only a slight rise in acidity. The significance of these and other changes produced by antrectomy have been discussed in a previous communication.[12] It is believed that lessened parasympathetic activity and the synergistic relationship between acetylcholine and histamine[9] underlie this phenomenon.

Comparison of the three groups of patients that had vagotomy reveals some interesting differences that are probably significant from a surgical viewpoint. After vagotomy with posterior gastroenterostomy, histamine stimulation produces an increase in volume and a threefold increase in acidity. The

major effect of this operation is interruption of preganglionic parasympathetic nerve supply. After vagotomy with antrum exclusion and gastroenterostomy, histamine stimulation causes only a slight rise in acid concentration and no increase in volume. Following vagotomy, antrum excision (hemigastrectomy), and gastroenterostomy, there was a decrease in volume and slight rise in acidity. Evidence concerning the effect of transection of the stomach upon the secretory activity of the parietal cell area has been considered in another report,[11] and the conclusion was reached that lessened secretory activity probably resulted from interruption of postganglionic parasympathetic fibers passing from the distal to the proximal parts of the stomach. If these concepts of the effects of various operative procedures are correct, decreased acid producing activity of the parietal cell area can be correlated with decreased acetylcholine liberation at postganglionic parasympathetic terminals. During histamine stimulation there appears to be a critical level of parasympathetic activity necessary to elicit the usual response to this drug,[3] and if insufficient innervation remains the effect of histamine stimulation will be the reverse of normal as far as volume is concerned. Another factor of possible importance is the antagonistic effect of epinephrine. It has been shown that epinephrine is released from the adrenals following histamine administration.[6] After operations which lessen acetylcholine release at parasympathetic terminals, the effect of circulating epinephrine may exert a more pronounced action on the vasculature of the stomach than it does under more normal circumstances. This concept of an antagonism between histamine-acetylcholine on one hand and epinephrine on the other is consistent with the results of Alley who observed the inhibitory effect of histamine on gastric secretion in dogs.[1] Secretion stimulated by sham feeding or the ingestion of food was inhibited by a prior injection of histamine. The effect was more pronounced in the case of sham feeding.

The possibility of a practical application of these phenomena has been explored and at present at least one approach appears promising. If one examines those operations that appear reasonably successful in the control of duodenal ulceration, namely, subtotal gastrectomy, vagotomy with posterior gastroenterostomy, vagotomy with hemigastrectomy, and vagotomy with antral exclusion and gastroenterostomy, each has in common the reversal of the volume stimulating effect of insulin stimulation described above. Conversely, in the reports of Farmer and associates[5] and in our own experience it can be seen that in those cases in which operation for duodenal ulcer has failed because of recurrent ulceration, the subjects responded to insulin hypoglycemia with increased volume of gastric secretion as compared to basal periods of collection. If the above interpretation of this phenomenon is correct, this indicates that sufficient cholinergic innervation remains after operation to give a predominant secretory effect on central stimulation, whereas after a successful operation, the reverse is true.

In an attempt to form a preliminary impression of this method of evaluating the effect of operation, the results of 3-hour Hollander tests on 50 patients that had antral exclusion–vagotomy operations 6 to 12 months previously have been examined. There have been no recurrent ulcerations in this group of patients. In the 50 tests performed the average volume per hour of gastric contents recovered during insulin hypoglycemia was less than the preceding basal period in 49 patients and in the other patient the volume recovered amounted to 68 ml. in the basal period and 76 ml. per hour following insulin administration. It thus appears that, with the accumulation of more data, clinical application of information of this sort may be anticipated.

SUMMARY

The gastric acid secretory response to histamine and insulin hypoglycemia in ulcer patients with intact stomachs and after various operations on the stomach have been considered. After partial gastrectomy and operations that depend on vagotomy for control of acid secretion, histamine does not produce the usual increase in volume and in some instances the volume of secretion is diminished. Similarly insulin hypoglycemia causes a lessening of volume after partial gastrectomy and vagotomy operations, whereas in the patients with intact stomachs the volume rises. The significance of these observations is discussed and the conclusion reached that diminished acetylcholine liberation from autonomic nerves is the common feature of those operations in which the reported effects are observed.

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A METHOD FOR THE CONTINUOUS OR REPEATED DETERMINATION OF BLOOD VOLUME

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RECENT advances in surgical technique, especially in cardiac and radical abdominal surgery, have increased the magnitude of ancillary problems in the technical management of the patients undergoing these procedures. One of these problems concerns the necessity of maintaining the blood volume of seriously ill patients.

A method of measuring blood volume is required which could be used in the operating room and be performed with sufficient rapidity to permit repeated determinations of blood volume throughout a major surgical procedure. This method would be particularly helpful in patients undergoing cardiac surgery where there may be acute and massive blood loss and in whom accurate and rapid blood replacement is essential. The existing methods of maintaining a normovolemic state by clinical evaluation and by the estimation of blood loss by weighing sponges and visual estimations of other losses have been helpful but are not always sufficiently reliable.

A method for the continuous or repeated determination of blood volume has been developed which we believe will be suitable for clinical use in the operating room.

METHOD

The method of measuring blood volume which appears to be the most adaptable is the method employing radioactive chromium (Cr^{51}) by the use of sodium chromate since erythrocytes are labeled in a stable fashion with this method.[1-3] Throughout our experiments the technique used for tagging of cells was that described by Talbot and associates.[4]

Our method for the repeated determination of blood volume requires the use of an extracorporeal circuit through which blood continuously circulates in the counting chamber of a well type of scintillation counter. If this blood contains radioactive chrominum-tagged erythrocytes, a definite counting rate is established as the blood passes through the counter. When a small measured volume of untagged blood is added to this system, the resulting dilution causes a decrease in the counting rate. This change in the counting rate is

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proportional to the volume of blood added and to the volume of the system to which it is added. The blood volume can then be calculated from these values.*

Our initial experiments with this method measured a volume of blood contained in a reservoir. Since this volume was known, the accuracy of the method could be checked. These in vitro studies showed the average error of the method to be ∓ 4.8 per cent in approximately 50 separate determinations.

In the in vivo experiments using 15 to 25 Kg. mongrel dogs an extracorporeal circuit was designed (Fig. 1). The femoral vein was cannulated with a plastic cannula. Blood flowed from the vein through a peristaltic action pump and was then circulated through a closed counting tube in the counting chamber of a well type of scintillation counter and returned to the animal through a plastic cannula into the external jugular vein. The experimental animals were heparinized by the intravenous administration of heparin (1.0 to 1.5 mg. kilogram). Plasticized vinylite tubing was used in all parts of the circuit except for the closed counting tube which was made of Teflon. The tubing which passed through the pump was cushioned with amber gum rubber tubing in order to minimize hemolysis caused by the action of the pump.

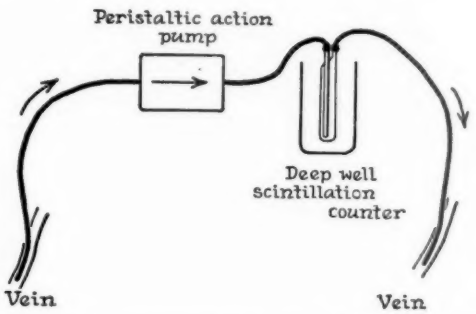

Fig. 1.—Diagrammatic representation of the extracorporeal circuit.

Blood flow in the extracorporeal circuit was maintained at a rate of 100 to 300 ml. per minute in all experiments. Changes in the blood volume of the dogs were produced by either bleeding or transfusing with whole blood.

At the beginning of each experiment 30 to 50 ml. of a radioactive chromium-tagged erythrocyte suspension were injected into the animal. A routine static blood volume determination was performed by removing several samples of blood after adequate mixing had occurred. This value for blood volume was then used as a standard for comparison with the blood volumes calculated by the new method. The volume of the added increments which produced the dilution amounted to approximately 3 to 5 per cent of the estimated total blood volume of the animal. Fig. 2 shows the necessity of adding this amount in order to maintain the statistical error within 5 per cent.

*Equation for calculating blood volume:

$$V_1 = \frac{\Delta V \times N_2}{\Delta N}$$

where V_1 = the initial blood volume before dilution,
ΔV = the volume of the added increment of untagged blood,
N_2 = the counting rate after dilution, and
ΔN = the change in the counting rate produced by the dilution.

Fig. 3 is a graphic representation of the amount of Cr^{51} which is required to produce a sufficiently high counting rate (75,000 to 100,000 counts per minute) to allow for accurate calculation of blood volume in 5 minutes' time. These calculations are made with a scintillation counter that has a sensitivity of 8 by 10^4 counts per minute per microcurie of Cr^{51} contained in a volume of 5 ml. with a background count of 120 to 150 counts per minute.

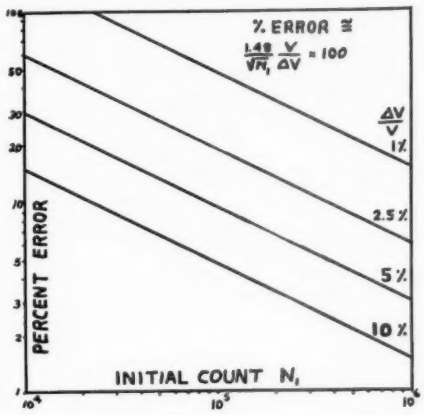

Fig. 2.

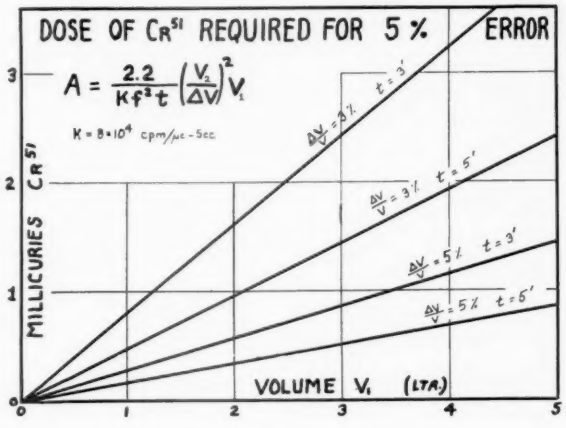
DOSE OF Cr⁵¹ REQUIRED FOR 5% ERROR
A = 2.2/Kf²t (V₂/ΔV)² V₁
K = 8×10⁴ cpm/μc-Sec
ΔV/V = 3% t = 3'
ΔV/V = 3% t = 5'
ΔV/V = 5% t = 3'
ΔV/V = 5% t = 5'
MILLICURIES Cr 51
VOLUME V₁ (LTR.)

Fig. 3.

Fig. 2.—Statistical error to be expected with changes in the total initial count (N_1), and changes in the ratio of the added increment to the total volume being measured ($\Delta V/V$).

Fig. 3.—Dosage of Cr^{51} required in order to limit statistical error to 5 per cent, where: V_1 is the initial volume before dilution; ΔV, the volume of the added increment of untagged blood; V_2, the volume after dilution; A, the millicuries of Cr^{51} required; K, the sensitivity constant for Cr^{51} of the scintillation counter used; t, the time in minutes; and f, the standard error.

EXPERIMENTAL DATA

More than 100 separate determinations of blood volume were performed in 15 dogs. In 4 of these animals the blood volumes were performed as parts of other types of experimental studies and these results will not be discussed in this report. The initial static blood volume performed during each experiment served as a standard for comparison with the blood volume calculated by the new method. Table I shows the correlation between the two methods.

TABLE I.

DOG NO.	VOLUME CALCULATED BY STATIC METHOD	VOLUME CALCULATED BY CONTINOUS FLOW METHOD	PERCENTAGE ERROR
1	1818	1791	−1.5
2	2327	2193	−5.8
3	1741	1730	−0.6
4	1756	1706	−2.8
5	1598	1633	+2.2
6	1442	1460	+1.2
7	1530	1570	+3.7
8	1714	1661	−3.1
9	1736	1703	−1.9
10	2877	2701	+6.1
11	1172	1148	−2.0

Throughout the remainder of each experiment the animal was successively bled or transfused, and the volume calculated by the continuous flow method was compared to the expected volume based on the original standard static volume, plus or minus the change in volume due to either bleeding or transfusing. Two such experiments are shown diagrammatically (Figs. 4 and 5). The variance between the expected volume and the volume found by the continuous flow technique is expressed as the percentage error.

In over 100 separate determinations of blood volume by these methods, the average error was 3.2 per cent with the maximum error of any single determination of 9.3 per cent.

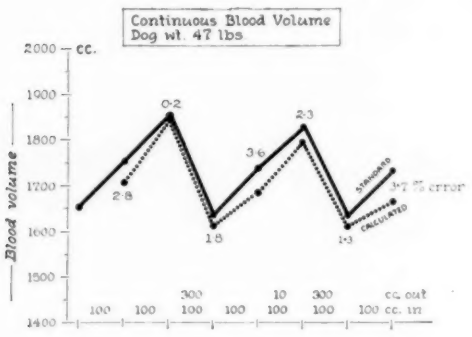

Fig. 4.

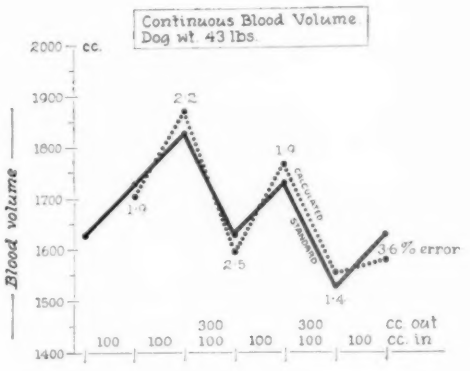

Fig. 5.

Figs. 4 and 5.—Diagrammatic representation of an in vivo experiment. The solid line is the expected blood volume and the dotted line is the blood volume measured by the continuous flow technique. The difference between the two figures is expressed as the percentage error.

No serious hemolysis was found after flow through the external circuit using the peristaltic action pump. The maximum plasma hemoglobin found in any animal was 0.146 Gm. per cent and this was determined after 6 hours of continuous pumping of blood through the extracorporeal circuit. At the conclusion of the experiments no significant changes were found in the serum sodium, potassium, or chloride levels of the experimental animals.

SUMMARY

1. A new method for the continuous or repeated determination of blood volume is described. In over 100 separate determinations of blood volume in dogs, the average difference between the blood volume calculated by this method and that measured by the routine static blood volume using Cr^{51} was 3.2 per cent.

2. This method appears to be applicable for use in the operating room with those patients in whom it would be advantageous to know the circulating blood volume at any moment during a surgical procedure. If the counting rate of the blood flowing through the extracorporeal circuit is maintained at a sufficiently high rate, an accurate calculation of blood volume can be obtained in 5 minutes with the patient still undergoing the surgical procedure, irrespective of the amount of blood lost or transfused prior to this period of measurement.

3. The correlation of the blood volume calculated by this method and that measured by the routine static method has been satisfactory, and a preoperative blood volume could be used as a reference value for maintaining the blood volume throughout a surgical procedure.

4. This method appears to be especially adaptable for use with this artificial oxygenator or kidney since it could be incorporated directly into the extracorporeal circulation.

We gratefully acknowledge the technical assistance given this project by Miss Alice Cary.

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SHOCK: A SURGICAL HAZARD IN THE PARAPLEGIC

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WHEN the literature dealing with paraplegia is studied, one is immediately impressed by the number and variety of complications suffered by these individuals. The frequent occurrence of renal disease and decubitus ulcers is common knowledge. The frequent occurrence of metabolic disorders[4] (protein catabolism, decreased serum proteins, altered liver function, lowered basal metabolic rate, gynecomastia, testicular atrophy, and menstrual disorders), autonomic hyperreflexia,[9] venous occlusion,[1] and amyloidosis[6] is less well known. The frequent occurrence of shock during surgery in paraplegics was not appreciated by us and is not prominently mentioned in the literature. The following case reports emphasize the significance of this hypotensive tendency.

CASE REPORTS

CASE 1.—P. H. (V.A. C-52871), a 57-year-old white man, had transverse myelitis in 1941 and had been a paraplegic since that time. Numerous procedures had been performed previously, including cystoscopies, rotation of flaps for decubitus ulcers, and so forth. During the present admission, the patient had undergone prolonged conservative treatment for decubitus ulcers which was without notable success. He was transferred to surgery for a rotational flap for a decubitus ulcer present between the buttocks and thigh on the right side. Hemoglobin prior to surgery was 13 Gm. Anesthesia was unnecessary for the surgery which consisted of outlining a flap and moving it upward into the excised defect of the decubitus ulcer. Midway through the procedure the patient stated that he felt nauseated. He was pale, cold, and perspiring profusely with no obtainable blood pressure. At this point, the procedure was terminated. It was estimated that a blood loss of 500 c.c. had occurred. The patient was transfused with 1,500 c.c. of whole blood, and 15 mg. of Vasoxyl was administered. The pressure responded and continued to be within normal limits. The hemoglobin obtained shortly afterward was 14 Gm. Recovery was uneventful.

CASE 2.—J. W. (V.A. C-4290963), a 30-year-old white paraplegic, was admitted with multiple decubitus ulcerations of the buttocks and hips. He had sustained his paraplegia in an automobile accident 3½ years previously, with a D-7 myelopathy resulting. The decubitus ulcers were treated in the usual fashion and, after they had healed sufficiently, the patient agreed to have both of his useless lower extremities amputated. The hemoglobin on admission was 10 Gm. (63 per cent) and his status otherwise was satisfactory. The blood volume deficit was corrected by multiple transfusions, and, on Dec. 5, 1955, amputation of the right femur was carried out with no consequences and an uneventful postoperative period. After the preanesthetic medication had been given on Dec. 27, 1955, prior to amputation of the left lower extremity, the blood pressure dropped to 88/58. Despite the hypotension, the patient was anesthetized and continued to exhibit a blood pressure of 88/58. Fifteen milligrams of Vasoxyl were given and the pressure climbed to 120/80 where it

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remained. The left lower extremity was amputated, 1,500 c.c. of whole blood were administered during the latter part of the procedure and the postoperative period, and the patient experienced an uneventful recovery. The hemoglobin prior to the last procedure was 12 Gm. (70 per cent).

CASE 3.—F. T. (V.A. C-11970570), a 66-year-old white man, had suffered a lower dorsal myelopathy one year previously. The present admission was necessitated by chills and fever. He was found to have calculi in the bladder with spasticity of the bladder and chronic cystitis. Admission hemoglobin was 12 Gm. (75 per cent). Approximately 1½ months after admission a transurethral resection was done because of bladder neck obstruction. After 45 minutes of anesthesia, which consisted of pentothal, nitrous oxide, and oxygen, the blood pressure dropped from 110/60 to 50/30. Ephedrine, 25 mg., was administered with a prompt and sustained blood pressure following. Little bleeding was encountered during the procedure and the hemoglobin following surgery was 11 Gm. (69 per cent).

CASE 4.—A. A. (V.A. C-17474581) was injured in an automobile accident in September, 1952, sustaining fractures of the sixth and seventh cervical vertebrae with a resulting transverse myelopathy at C_6. Since that time he had been admitted on several occasions for treatment of genitourinary tract infections. Chronic pyelonephritis and urethral perineal fistulas necessitated his present hospitalization. On admission the hemoglobin was reported as 13.5 Gm. with 4,370,000 red blood cells. Urine culture showed a large growth of *Proteus vulgaris* and hemolytic *Staphylococcus albus*. An indwelling Foley catheter was inserted and the urinary tract infection was treated with antibiotics and fluids. One month after admission an attempt was made to remove the Foley catheter. The bulb failed to deflate and, after all the usual methods had been exhausted, it was necessary to perform a suprapubic cystotomy to deflate the bulb directly. Anesthesia consisted of pentothal, nitrous oxide, and oxygen and, at the end of the short relatively atraumatic procedure, the patient's blood pressure was stable at 130/76, as it had been during the entire procedure. While the patient was being turned, his blood pressure suddely dropped to 60/34. No evidence of bleeding nor any cause for the sudden drop in blood pressure could be determined. The blood pressure responded to the intravenous use of Levophed and within 30 minutes the patient was warm and alert. The postoperative course was uneventful. The postoperative hemoglobin was recorded as 15 Gm. with 4,600,000 red cells.

DISCUSSION

Incidence.—Our interest in the problem of shock in surgery of paraplegics was stimulated by the alarming reaction in Case 1 to such minimal trauma. Since the surgical problems of this unfortunate group are handled by a number of the surgical specialties, the various members were questioned regarding shock in paraplegics. It was found that each had experienced similar, though less frightening, episodes of hypotension. Apparently this was not thought significant because of the relatively small number of paraplegics requiring surgery and because of the wide distribution of the cases between the various specialties. However, when the number of cases of hypotension in paraplegic surgery was compared with the total number of paraplegic surgical cases, a 57 per cent incidence of hypotension or shock was recorded. The incidence of shock or hypotension in nonparaplegic surgery cases at this institution is not known but certainly does not approach this astounding figure of 57 per cent.

Surprising as the incidence of hypotension was, we were even more perplexed when we were unable to find the complication seriously considered in

the literature. Admittedly, the preoperative preparation was less than ideal in a number of cases but hardly so different from that in other centers that we would not expect to see literary references to the complication.

Mechanism.—If shock in paraplegics is more frequent than in surgery of nonparaplegics, the mechanisms of this complication deserve some thought. Pollock and associates[8] pointed out the similarity of skeletal muscles deprived of their spinal efferent nerves and of sweat glands, smooth muscle, and blood vessels deprived of their sympathetic innervation. Just as motor paralysis follows in skeletal muscles below the injured segment so does paralysis occur in sympathetic innervated structures. When normal man assumes an erect position blood gravitates to those structures below the level of the heart. Due to engorgement and distention of the splanchnic bed and lower extremity vessels, compensatory vasotonic and vasoconstrictor impulses arise which regulate the intravascular blood volume shift. In spinal cord injuries there is paralysis of central vasotonic and vasoconstrictor impulses with resulting orthostatic hypotension. The degree of orthostatic hypotension is such that in 8 of 10 of Pollock's paraplegic patients unconsciousness resulted from cerebral anemia when they were tilted from the horizontal to the vertical position.

This attractive mechanism might explain in whole or in part the hypotension occurring in Case 4—hypotension as a result of moving the patient. However, it fails to account for the remainder of the hypotensive episodes.

If we would use the orthostatic hypotension mechanism in combination with blood loss another plausible explanation is evident. One recalls that following blood loss vasoconstriction results in an effort to maintain normal hemodynamics. This defense mechanism is activated relatively early during hemorrhage and without any further large blood loss in an efficient long-lasting one. In the paraplegic patient this protective response to intolerable blood loss is lacking in that part of the organism below the spinal cord lesion, and the affected vascular bed is unable to respond by vasoconstriction. The amount of response will depend upon the level of the myelopathy—the higher the lesion, the less vascular bed capable of vasoconstriction. Chor, Finkelman, and Blustein[2] demonstrated the relationship of basal blood pressure in paraplegics to the level of the spinal cord injury and it is interesting to note that the blood pressure in their quadriplegic patients was frequently as low as 78 mm. systolic and 50 mm. diastolic.

The most plausible explanation for our hypotensive experiences, at least, is a combination of the previously discussed mechanisms with an initial significant blood volume deficit: inability of the vascular bed to respond normally to blood lost from an already depleted reservoir. It must be kept in mind that these individuals are chronically ill, many with open, infected, draining ulcers, many with urinary tract infections, and many with a whole host of other complications. They lose a tremendous amount of weight initially[2] and with few exceptions fail to regain that loss. They suffer a great nitrogen loss during the early period of their injury, and it is not unusual for this catabolic stage to last up to 14 months.[4] They have difficulty maintaining a respectable

serum protein level and their hypoproteinemia persists despite high protein intake for long, variable periods of time. This chain of events sets the stage perfectly for what Lyons[3] called "chronic shock" several years ago—inadequate blood volume. Unfortunately, blood volume determinations in these paraplegic patients were not carried out and it is erroneous to attempt to draw any conclusions concerning blood volume from the red blood cell count, hemoglobin, or hematocrit determinations.[7] However, if we use these laboratory procedures as they are generally employed in determining blood replacement it will be seen that at least 3 of the 4 cases were in need of blood replacement even by these indices.

Significance.—The occurrence of severe hypotension or shock in an otherwise healthy individual is a serious matter. Its occurrence in a paraplegic assumes even more serious proportions. Two reasons for this statement stand out foremost in our minds at this time.

1. The care of paraplegics today is such that a great many of these people will live to the age when they will be exposed to the added hazard of coronary artery disease. As each year passes, the ranks of the paraplegics are thinned by the already well-emphasized complications, but many of the "young" ones will live to the "coronary age" to join those who suffered their paraplegia at an already advanced age. The fact that the myocardium, laboring under the burden of marginal blood supply in coronary artery disease, is particularly intolerant to any added depriving insult is well known. Shock or hypotension with its decreased coronary flow is indeed a serious burden and could well be a final insult in those patients with coronary artery disease.

2. Lord and Bunts[5] found that in a recent 10-year follow-up of World War II paraplegics that renal disease was responsible for one-third of the deaths in paraplegics, when deaths due to violence were excluded. Infection, stasis, immobilization, and hypercalcinuria all promote calculosis and narrow the functioning kidney margin. Any decrease in renal blood flow as a part of the shock syndrome could seriously affect kidney function and might tip the balance adversely.

As is the case with many complications in surgery, the majority of the complications suffered by paraplegics are almost impossible to prevent. Unlike the others, the occurrence of shock during surgery in paraplegics is preventable for the most part. Of course, the one way to escape with a minimum of complications is to be aware of the possibility and of the altered physiology leading to the complication. In the paraplegic it must be remembered that we are dealing with an individual whose entire physiology has been greatly altered and not with an isolated decubitus ulcer, bladder calculus, or whatever the indication for surgical attack. The fact that the patient is in reality a chronically ill individual must be constantly remembered. His serum proteins and blood volume should receive particular attention with complete replacement of any deficit preoperatively. Although we are incapable of improving the response of his vascular bed, if the patient goes to surgery with a normal blood volume and blood loss is replaced promptly, there will be no need for his vascular

bed to respond by vasoconstriction, for this is a response elicited by a significantly reduced blood volume. These fundamental precautions combined with the use of vasopressor agents, if need be, should prevent the occurrence of hypotension or shock during surgery in paraplegics.

SUMMARY

1. Four paraplegic cases subjected to relatively minor surgical trauma suffered shock. These 4 patients represent 57 per cent of all paraplegics operated upon at this institution.

2. The more frequent occurrence of shock in paraplegics than in non-paraplegics is suggested as still another complication to swell the already long list suffered by paraplegics.

3. The inability of the vascular bed to respond by vasoconstriction to blood loss in an individual with a blood volume deficit is suggested as the mechanism of shock in these patients.

4. The need of the paraplegic as a chronically ill individual for careful preoperative evaluation of blood volume replacement is emphasized.

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ADRENOCORTICAL RESPONSE TO SURGERY

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SURGICAL trauma is followed by a succession of metabolic events among which is a rise in the level of plasma corticosteroids.[15, 32, 35] The main corticosteroid component, 17α-hydroxycorticosterone, is conjugated in the liver and excreted in the urine. In individual patients the plasma and urinary corticoid patterns have been fairly well investigated.[14, 15, 17, 18, 19, 21, 22, 26, 27, 32, 35] The purpose of this paper is to illustrate the range in amount and duration of the increase in the urinary excretion of total 17-hydroxycorticosteroids following major and minor surgical trauma in a group of 48 male patients. Some understanding of the range of operative response is required before abnormalities in adrenocortical secretion or of tissue utilization can be recognized.

METHODS

These investigations cover 19 male patients submitted to partial gastrectomy for chronic peptic ulceration, 16 undergoing inguinal herniorraphy, and 13 explored for carcinoma of the stomach. The anesthesia (intravenous thiopentone and curare, and endotracheal nitrous oxide and oxygen) and the postoperative management were as far as possible standardized. Patients were not confined to bed before and usually not longer than 2 or 3 days after operation. Urine, voided by the patient, was collected in 24-hour batches and stored without preservative until assayed. The total 17-hydroxycorticosteroids were estimated by Norymberski's technique and expressed as milligrams per 24 hours. Duplicate assays were performed and were repeated if the discrepancy was greater than ± 5 per cent.

The response to operation will be expressed in 3 ways: (1) the duration of raised urinary excretion, (2) the day of maximal excretion, and (3) the mean urinary corticoid excretion for the first 4 postoperative days (4-day mean). This last enables a quantitative comparison to be made between individual cases.

The total 17-hydroxycorticosteroid excretion in normal subjects depends on age[7, 25, 33] and weight,[7] the 95 per cent range for men falling from 5.7 to 21.0 mg. per 24 hours at 30 years to 2.9 to 12.7 mg. per 24 hours at 80 years (Borth[7]). Appleby and associates[1] state that in the majority of cases and in the absence of increased 21-deoxy-17:20 ketols (for example, the adrenogenital

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TABLE I. PARTIAL GASTRECTOMY

CASE NUMBER	INITIALS	AGE (YR.)	PATHOLOGY	PREOPERATIVE MEAN (MG./24 HR.)	DURATION (DAYS)	MAXIMAL OUTPUT (MG./24 HR.)	DAY OF MAXIMAL OUTPUT	4-DAY MEAN (MG./24 HR.)	CONVALESCENCE
1	D. P.	37	CDU	—	7	50.4	1, 2, 3	45.0	Uneventful
2	C. E. G.	62	CDU	16.1	4	60.6	1	42.1	Uneventful
3	A. W.	43	CGU	13.7	6	58.5	3	41.2	Uneventful
4	H. K.	69	CDU	—	4	55.5	3	35.2	Shock, pulmonary collapse, bronchoscoped
5	E. R. W.	35	CDU	11.6	(4)*	47.2	3	34.9	Died sixth day: internal strangulation
6	T. B.	48	CDU	12.3	2	45.2	1	28.5‡	Uneventful
7	A. S.	59	CDU	—	6	33.0	3	27.9	Uneventful
8	H. B.	51	CDU	14.4	4	34.4	2	27.5	Uneventful
9	E. A. E.	45	CDU	10.1	7	40.4	3	27.4	Abdominal pain: N.Y.D. fourth day
10	H. R.	43	EGS	—	4	36.2	3	26.0	Dehydrated: I.V. fluids 3 days
11	C. M.	44	CGU	14.4	2/3†	56.4†	2†	24.4†	Shock, blood, Methedrine
12	C. M.	43	CDU	—	5	30.2	3	23.2	Dehisced abdominal wound twelfth day
13	L. S.	56	CDU	14.0	6	24.8	2	23.0	Uneventful
14	R. E.	51	CDU	—	5	40.8	3	21.3	Uneventful
15	F. C. C.	66	CDU	12.2	3	41.2	2	21.2	Uneventful
16	A. A.	67	CGU	—	3	33.1	2	20.9	Uneventful
17	C. H.	44	CDU	11.1	3	32.1	2	19.6	Uneventful
18	F. H.	60	CGU	—	3	24.0	1, 2	19.1	Uneventful
19	M. P.	41	CDU	11.9	2	22.2	2	15.7	Uneventful
			Mean	12.9	4.3	40.3	2, 3	27.6	
			S.D.§	1.7		12.0		8.3	
			Range	10.1	2	22.2	1	15.7	
				16.1	7	60.6	3	45.0	

CDU = chronic duodenal ulcer.
CGU = chronic gastric ulcer.
EGS = eosinophilic granuloma of stomach.
*Urine collection for 4 days only.
†Third specimen lost.
‡Three-day mean, ACTH given on fourth day.
§S.D. $\times \sqrt{n/n-1}$.

syndrome) the total 17-hydroxycorticosteroid output is equivalent, within the limits of experimental error, to the results obtained by the ketogenic steroid technique.[28] Levell and co-workers,[25] employing the latter technique, reported a normal 80 per cent range of 8.0 to 21.0 mg. per 24 hours at 30 years falling to 5.0 to 12.5 mg. per 24 hours at 80 years.

RESULTS

The range of the individual mean preoperative excretions of total 17-hydroxycorticosteroids in 27 of the male patients free from carcinoma was 8.4 to 16.2 mg. per 24 hours (mean 12.9 mg., S.D. 2.2 mg.). The fluctuations from day to day in any one normal individual may be considerable, and in this paper it is assumed that the operative response is ended when the daily excretion falls below the upper limit of the preoperative range, that is, 16.2 mg. per 24 hours.

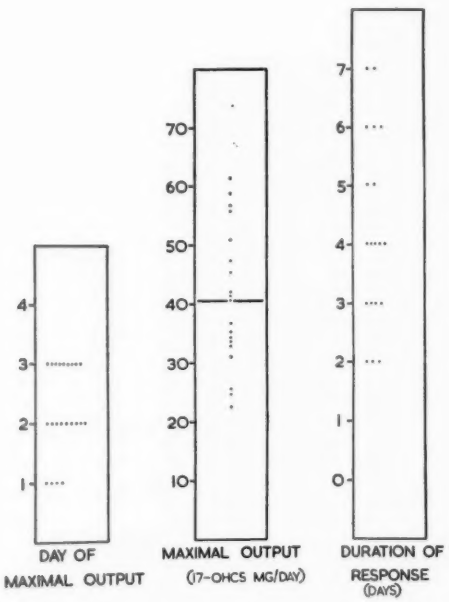

Fig. 1.—Showing total 17-hydroxycorticosteroid response to partial gastrectomy. Each dot represents one patient.

The Effects of Age and Severity of Operation.—The major operation chosen for this study was partial gastrectomy (Table I). In this group of 19 patients whose ages ranged from 35 to 67 years, 14 had chronic duodenal ulcers, 4 had chronic gastric ulcers, and one had an eosinophilic granuloma of the stomach. They were all otherwise in good health except for H. K. (No. 4) who was dehydrated and anemic. Before operation the corticoid output of this group was 10.1 to 16.1 mg. per 24 hours (mean 12.9 mg., S.D. 1.7 mg.). The increased corticoid excretion (that is, above 16.2 mg. per 24 hours) lasted for 2 to 7 days (mean approximately 4 days) (Fig. 1). The maximal daily output showed a wide degree of scatter with a range of 22.2 to 60.6 mg. per 24 hours (mean 40.3 mg., S.D. 12.0 mg.) and occurred most commonly on the

TABLE II. INGUINAL HERNIORRAPHY

CASE NUMBER	INITIALS	AGE (YR.)	PATHOLOGY	PREOPERATIVE MEAN (MG./24 HR.)	DURATION (DAYS)	MAXIMAL OUTPUT (MG./24 HR.)	DAY OF MAXIMAL OUTPUT	4-DAY MEAN (MG./24 HR.)	CONVALESCENCE
20	S. C. H.	31	LIH	15.1	5	44.6	1	29.7	Uneventful
21	A. L.	44	RIH, UH, Hy.	14.5	3	30.7	2	22.7	Uneventful
22	E. N. G.	38	RIH	12.5	3	24.3	1, 2	20.3	Uneventful
23	J. A. L.	46	RIH	14.6	3	36.9	2	20.0	Uneventful
24	J. L.	60	LIH	14.7	4	21.8	2	19.9	Hematoma of wound
25	P. D.	47	BIH	12.8	3	27.4	2	19.6	Uneventful
26	J. G.	33	BIH	16.0	5	22.8	2	18.4	Uneventful
27	B. S.	69	LIH, Orch.	12.7	5	26.0	2	17.5	Uneventful
28	F. J.	56	LIH	12.8	3	21.0	3	17.3	Uneventful
29	R. S.	59	RIH	14.0	4	25.6	4	15.2	Cough and pyrexia—7 days
30	J. O.	19	RIH	13.8	2	22.1	1	15.0	Uneventful
31	H. H.	47	BIH	8.4	2	25.0	2	13.9	Uneventful
32	E. E.	62	BIH, Circ.	8.6	2	17.2	2	13.6	Uneventful
33	M. C.	68	LIH, Orch.	11.0	1	16.4	1	13.6	Uneventful
34	C. S.	50	LIH	16.2	0	15.4	1	13.4	Uneventful
35	J. A. C.	68	RIH	9.2	1	16.6	1	11.9	Uneventful
			Mean	12.9	2.9	24.6	1.8	17.6	
			S.D.*	2.5		7.7		4.5	
			Range	8.4	0	15.4	1	11.9	
				16.2	5	44.6	4	29.7	

IH = repair of inguinal hernia (L, left; R, right; B, bilateral).
UH = repair of umbilical hernia.
Hy. = excision of hydrocele.
Orch. = orchidectomy.
Circ. = circumcision.
*S.D. $\times \sqrt{n/n-1}$.

second and third days after operation. The low incidence of first-day maxima may be in part due to the difficulty in obtaining complete bladder emptying in the first 24 hours. Urine which was not voided during this period would have been collected in the second 24 hours; this possible explanation of the high incidence of second-day maxima would not, however, explain the equally high incidence in the third period. The 4-day mean in this group was 15.7 to 45.0 mg. per 24 hours (mean 27.6 mg., S.D. 8.3 mg.). This is correlated with the age of the patient and also expressed as a percentage increase of the preoperative mean in Fig. 2. There is no tendency for the corticoid response after operation to decrease with increasing age. The 3 highest and the 7 lowest corticoid responses were accompanied by uneventful convalescence without any signs attributable to adrenocortical failure or overactivity. High responses occurred in 2 of the 6 patients in whom recovery was interrupted. One, H. K. (No. 4), aged 69 years, required bronchoscopy for acute respiratory obstruction and his condition was poor for the first 3 postoperative days; and the second, E. R. W. (No. 5), aged 35 years, developed signs of internal strangulation on the fourth postoperative day from which he died 2 days later.

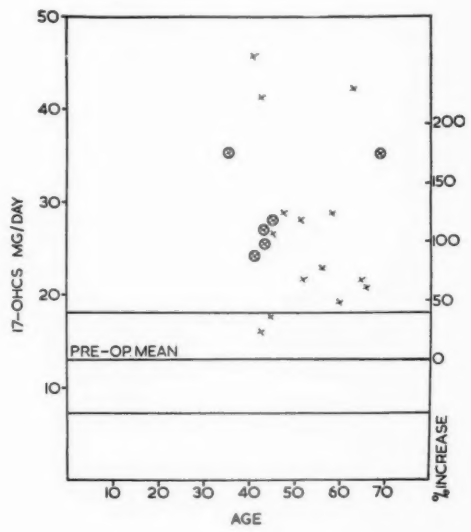

Fig. 2.

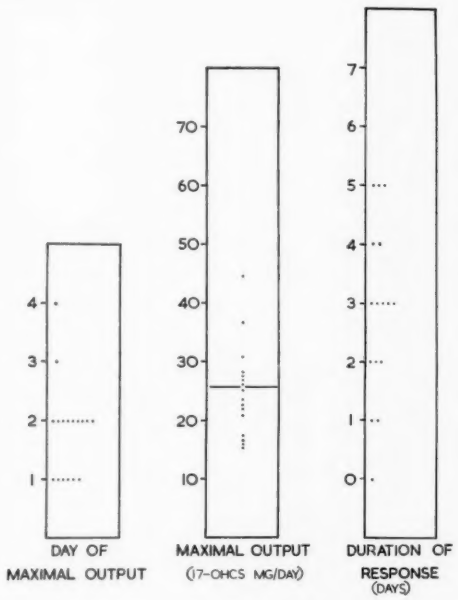

Fig. 3.

Fig. 2.—The preoperative mean and range of 17-hydroxycorticosteroid excretion (milligrams per 24 hours) is shown by the 3 horizontal lines. Each cross represents the mean 17-hydroxycorticosteroid excretion (milligrams per 24 hours) for the first 4 postoperative days in one patient. This is also expressed as a percentage increase of the preoperative mean. The ringed crosses indicate that convalescence was complicated.

Fig. 3.—Showing total 17-hydroxycorticosteroid response (milligrams per 24 hours) to inguinal herniorrhaphy.

The minor operation chosen for comparison was inguinal herniorraphy which was performed on one or both sides in 16 patients, aged 19 to 69 years (Table II); in 4 cases minor additional procedures were performed at the same operation. The corticoid output before operation was 8.4 to 16.2 mg. per

TABLE III. CARCINOMA OF STOMACH

	CASE NUMBER	INITIALS	AGE (YR.)	PREOPERATIVE MEAN (MG./24 HR.)	DURATION (DAYS)	MAXIMAL OUTPUT (MG./24 HR.)	DAY OF MAXIMAL OUTPUT	4-DAY MEAN (MG./24 HR.)	CONVALESCENCE
Partial gastrectomy	36	A. C.	67	9.5	3	36.4	1	26.8	Uneventful
	37	E. H.	50	8.5	3	37.4	3	23.5	Uneventful
	38	A. R.	48	8.4	3	37.2	1	22.5‡	Uneventful
	39	J. B.	59	—	7	36.6	4	13.4	Very slow recovery; vomiting; I.V. fluids
Gastroenterostomy	40	W. R.	60	16.4	8	78.0†	2†	45.5	Slow recovery
	41	R. N.	45	—	12	53.2	3	30.2	Ileus third to seventh day
	42	C. M.	57	—	1	26.8	1	15.6	Uneventful
	43	R. J.	68	15.8	0	16.4	3	10.9	Uneventful
Laparotomy	44	A. B.	55	20.0*	10	69.8*	4	51.2*	Slow recovery; wound dehisced thirteenth day
	45	M. W.	50	—	4	25.4	2	22.3	Deteriorated and died thirteenth day
	46	M. F.	74	18.0	6	22.0	5	15.0	Almost moribund; very slow recovery
	47	M. T.	51	10.0	2	18.5	2	14.7	Slow recovery
	48	F. R.	71	8.9	0	14.3	2	8.2	Slow recovery but general condition deteriorating

*Ketogenic steroids.
†First specimen lost.
‡Second specimen lost.

24 hours (mean 12.9 mg., S.D. 2.5 mg.). One patient showed no significant postoperative rise (that is, above 16.2 mg. per 24 hours) and in the remainder the response lasted up to 5 days (Fig. 3). The 4-day mean was 11.9 to 29.7 mg. per 24 hours (mean 17.6 mg., S.D. 4.5 mg.). Seven of the 16 patients failed to have a 4-day mean as high as 16.2 mg. per 24 hours. The maximal daily output was 15.4 to 44.6 mg. per 24 hours (mean 24.6 mg., S.D. 7.7 mg.) and, with two exceptions, all occurred on the first or second postoperative day. No correlation could be found with age (Fig. 4).

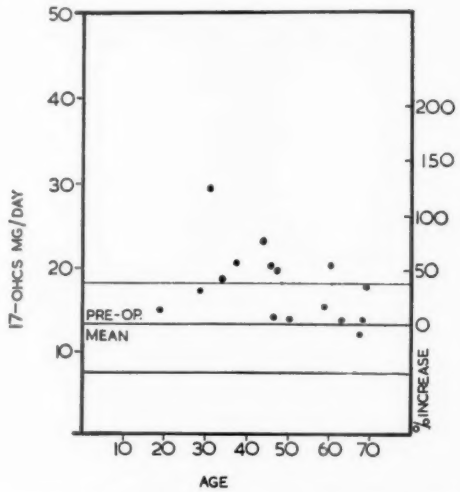

Fig. 4.—The preoperative mean and range of 17-hydroxycorticosteroid excretion (milligrams per 24 hours) is shown by the 3 horizontal lines. Each dot represents the mean 17-hydroxycorticosteroid excretion (milligrams per 24 hours) for the first 4 postoperative days in one patient. This is also expressed as a percentage increase of the preoperative mean.

The Effects of Malignancy and Cachexia.—Thirteen patients with gastric carcinomas were selected for this study (Table III). Four (48 to 67 years) of these were reasonably fit with resectable growths and were submitted to partial gastrectomy. Convalescence was uneventful except in J. B. (No. 39) who required postoperative intravenous saline because of vomiting. Their preoperative output was 8.4 to 9.5 mg. per 24 hours, postoperative maxima were 36.4 to 37.4 mg. per 24 hours and the 4-day mean was 13.4 to 26.8 mg. per 24 hours.

In 4 patients (45 to 68 years) gastroenterostomy was performed. The neoplasm was not resected because of its advanced state locally or because of metastases. Recovery was uneventful in 2, slow in the third, and associated with paralytic ileus in the fourth. Preoperative urine specimens were available from only 2 patients and gave corticoid outputs of 15.8 and 16.4 mg. per 24 hours. The maximal response of the group was 16.4 to 78.0 mg. per 24 hours and the 4-day mean 10.9 to 45.5* mg. per 24 hours.

Confirmatory laparotomy and biopsy were performed on 5 patients (50 to 74 years) with extensive local or disseminated lesions. Recovery after operation was slow in all cases; one patient died on the thirteenth day. In 3 patients the corticoid response was low (4-day means: 8.2, 14.7, and 15.0 mg.

*The first 24-hour specimen of this patient was lost. This maximal figure is therefore too low.

per 24 hours) and in the fourth was within the normal range (4-day mean: 22.3 mg. per 24 hours). The fifth patient, A. B. (No. 44),* was exceptional in that his 4-day mean figure was 50.1 mg. per 24 hours and the response persisted above 16.2 mg. per 24 hours until the tenth postoperative day. On the thirteenth day his wound dehisced.

DISCUSSION

Although a rise in the free 17-hydroxycorticosteriod plasma level is reported to persist for approximately 24 to 72 hours after operation,[15] neither its duration nor magnitude are necessarily true indices of adrenocortical function. The plasma level results from a balance between the rate of secretion, the volume of distribution,[36] the rate of conjugation and hydrogenation, the rate of destruction in the tissues, and the rate of excretion.[17] The volume of distribution probably diminishes with age[36] and the rate of conjugation with liver damage.[5, 6, 8, 13, 24, 37] The amount of free corticoid which is excreted in the urine is very small.[37]

The rise in the conjugated corticoid plasma level is later in onset and more prolonged than that of free corticoid and depends on the rate of conjugation and hydrogenation together with the rate of renal clearance.[6, 23] In patients with cirrhosis the rise in conjugated levels is delayed, lower, and more prolonged; in anuria a tenfold increase in the level is seen.[23, 24]

Tetrahydrocortisone is the corticoid metabolite contained in the greatest amounts in the urine[2] and its rate of excretion is dependent on the conjugated plasma level and the rate of renal clearance. In the normal patient there is evidence that the metabolites of oral or infused cortisone are rapidly excreted in the urine. After the oral administration of 100 mg. of cortisone the urinary corticoid output returns to normal in 16 hours.[28] Although high concentrations of corticoid metabolites occur in postoperative oliguria,[22] the total amount excreted during this period may be decreased. In the absence of hepatic or renal impairment the excretion of urinary corticoid metabolites provides a convenient and satisfactory measure of the length and intensity of increased adrenocortical activity after operation.

In this series the increased excretion of urinary corticoids following a major operation lasted from 2 to 7 days, thus confirming previous reports.[14, 17, 18, 19, 22, 26, 27] Although the corticoid response was prolonged beyond 4 days in 2 of the 5 patients (excluding E. R. W. [No. 5] who died on the sixth postoperative day) who developed postoperative complications, it was similarly prolonged in 5 of the 13 patients with uneventful convalescence. The frequent delay of peak excretion until the third day is not in accord with previous reports[14, 19, 22, 27] and might have been due to a combination of temporary hepatic dysfunction and oliguria. Further study of urinary corticoid excretion together with both free and conjugated plasma levels will be necessary to clarify this point.

The magnitude of the response as expressed by the 4-day mean varied from 15.7 to 45.0 mg. per 24 hours. We have been unable to correlate this widely differing behavior from patient to patient with other factors such as

*This case has been described in detail by Jepson and associates.[22]

physique and difficulty or length of operation. Intravenous infusions of corticotrophin similarly produce a wide range of maximal individual responses[3, 30] although these do not necessarily predict the response to surgery.[21] Moreover, in this series, there was no apparent correlation between the resting rate of corticoid excretion and the operative response. This is in accord with the statement of Dobriner[11] that the resting level is no indication of the ability of the adrenal cortex to respond to corticotrophin. For this reason expression of the results as a percentage increase over the resting level may be fallacious.

The less severe operation of inguinal herniorraphy was followed by a shorter and less marked corticoid response. The average 4-day mean was 17.6 mg. per 24 hours in contrast to 26.6 mg. per 24 hours for partial gastrectomy, although there was considerable overlap of individual responses (Fig. 5). This is not surprising as numerous cases have been reported in which there was no response to major surgery.[14, 18, 21, 22, 27, 32] Thus, as with many other postoperative metabolic changes such as those of sodium, potassium, and nitrogen, a wide variation in individual response is seen and is apparently compatible with an uneventful convalescence.

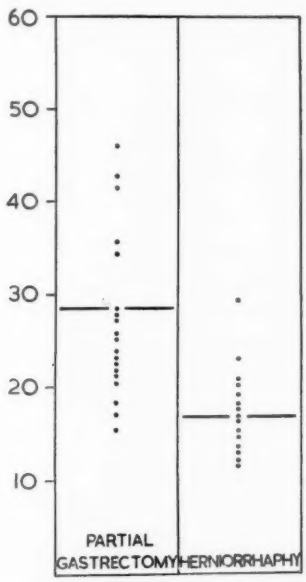

Fig. 5.—Each dot represents the 4-day mean 17-hydroxycorticosteroid excretion (milligrams per 24 hours) in one patient. Comparison between the response to partial gastrectomy and herniorrhaphy are shown. The horizontal lines in each column denote the mean excretion figure for each group.

With increasing age corticosteroid output is well maintained.[9, 17, 20, 29, 34] Levell and co-workers,[25] Schuller,[33] and Borth[7] show, however, that there is some regression in output in the aged; this may be due to their relative decline in normal activity and not reflect on their capacity for adrenocortical response. Similarly, response to corticotrophin is maintained in the aged,[3, 11, 12, 16] and Tyler and associates[36] found that plasma corticoid levels were even higher after the administration of corticotrophin in this group than in the young,

probably due to a smaller volume of distribution. In the present series there is no evidence of decreased ability of the adrenal cortex to respond with increasing age and, indeed, in association with malignant disease, very high outputs may be seen.

Patients with early malignant disease usually have a normal resting rate of corticoid excretion although the output of some of the patients in this series with more advanced lesions was at or above the upper limits of normal. This tendency has been previously reported[10, 17] and Rosenthal[31] has described a patient with advanced carcinoma of the lung with a ketogenic steroid output of 106 to 159 mg. per 24 hours. Apart from J. B. (No. 39) who excreted only 17.1 mg. corticoid in the first 72 hours after operation and whose recovery was very slow, the patients with lesions amenable to partial gastrectomy responded by corticoid excretion within the range described for benign ulceration. In those with advanced growths and cachexia a great and unpredictable variation in response occurred despite the decrease in severity of the operative procedures (Fig. 6). Debility and starvation have previously been reported

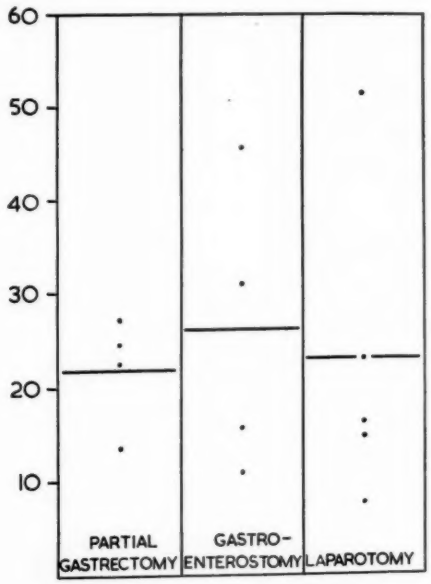

Fig. 6.—Comparison of the responses to partial gastrectomy, gastroenterostomy, and laparotomy in a group of patients suffering from carcinoma of the stomach. Each dot represents the 4-day mean 17-hydroxycorticosteroid excretion in one patient. The horizontal lines represent the mean excretion figure for each group.

to be associated with low responses[14, 17] and Gordon and associates[16] have suggested that decreased protein intake may result in decreased corticotrophin production in a similar manner to the decrease of gonadotrophin formation. However, in a few cases and especially the patient A. B. (No. 44) (previously reported by Jepson and co-workers[22]), very high responses have been seen after relatively minor trauma. This patient provides our only evidence of the possibly harmful effects of hypersecretion.

In this series, with the possible exception of J. B., there was no evidence that adrenocortical secretion had been inadequate. Franksson and co-workers,[15]

however, have reported 2 cases of postoperative shock associated with low plasma corticoid levels. We agree with Moore and associates[27] who maintain that although low excretion levels of 17-hydroxycorticosteroids are common, true surgical adrenocortical failure is rare.

SUMMARY

1. The urinary excretion of total 17-hydroxycorticosteroids has been studied in 19 adult male patients undergoing partial gastrectomy for benign peptic ulceration, 16 undergoing inguinal herniorraphy, and 13 explored for carcinoma of the stomach.

2. The preoperative corticoid excretion in 27 adult males free from carcinoma was 8.4 to 16.2 mg. per twenty-four hours.

3. Following partial gastrectomy there was an increase in corticoid output lasting 2 to 7 days, with a peak excretion of 22.2 to 60.6 mg. on the first, second, or third days. There was no evidence of decrease in response with increasing age. Postoperative complications were associated with either normal (4 patients) or high (2 patients) responses.

4. Inguinal herniorraphy was, in general, followed by a shorter and less marked response.

5. The response following exploration for advanced carcinoma of the stomach was very variable and unpredictable.

6. One patient with an unusually high response and one with an unusually low response are described.

7. There is a very wide range of adrenocortical response to surgery which is compatible with an uneventful convalescence.

We are greatly indebted to Dr. J. K. Norymberski for his valuable help and advice and to Mr. D. J. Bowen for technical assistance.

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THE INCIDENCE AND SIGNIFICANCE OF POLYPS OF THE COLON AND RECTUM

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THE high incidence of polyps discovered in patients examined at the Cancer Detection Center at the University of Minnesota Hospitals was noted in a previous communication.[6] The organization of the Center and the details of the examinations were elaborated in that paper, which reported the experience of the first 3 years' operation of the Center. A significant part of the examination includes a routine proctosigmoidoscopy after proper preparation and a double-contrast barium enema if any lesion is detected by proctosigmoidoscopy. This barium study, as well as the proctosigmoidoscopy, is repeated at each annual recheck visit if a polyp has once been discovered in the rectum or colon. Because of the high incidence of polyps discovered in these asymptomatic patients, 45 years of age and older, it seemed appropriate to carry out a review of the experience to date at this same Center to find out if the same number of polyps are being found in these patients and to find out if possible the fate and significance of these very frequent tumors.

The present review is concerned with the patients who were seen and examined at the Cancer Detection Center of the University of Minnesota Hospitals from March 1, 1948 through Feb. 29, 1956. During these 8 years, 7,608 patients were examined at the Center; a majority of them have been examined again at one or more annual follow-up visits. At the original examination, 876 (11.5 per cent) of the patients were found to have one or more polyps in the rectum and/or colon. In another 586 patients (7.7 per cent), rectal or colonic polyps were found on subsequent examinations, yielding a total of 1,462 patients (19.2 per cent) who exhibited rectal or colonic polyps on at least one examination. This is a slightly higher incidence than was reported in the earlier study (17.2 per cent). The observation that 11.5 per cent of asymptomatic patients, 45 years of age and older, exhibited these tumors compares well with the figures reported by Jackman and co-workers[9] who reported an incidence of 12 per cent and by Hauch and associates[7] who reported an incidence of 10 per cent in patients of this age group.

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In 1,459 patients, a total of 2,363 polyps* were discovered by proctosigmoidoscopy in the distal 25 cm. of large bowel. Another 90 polyps were discovered by double-contrast barium air enemas in 65 of these patients. In addition, 4 colonic polyps were discovered by barium examination in 3 patients who were studied for different reasons: occult blood in the stool, vague pains in the right lower quadrant, and proctitis. It is interesting that each of these last 3 patients was subsequently found to have a small polyp in the rectum. The distribution of all the polyps found by both methods of examination is shown in Figs. 1 and 2. All of these lesions were seen and recorded by the examiners as polyps, though some of them certainly were not true adenomas. Only 454 of the lesions seen at endoscopy were biopsied, and the results of these biopsies are shown in Table I. These biopsies represent the histology of

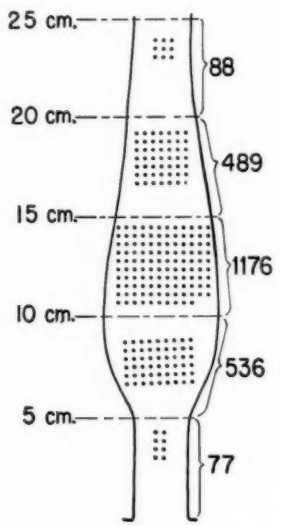

Fig. 1.

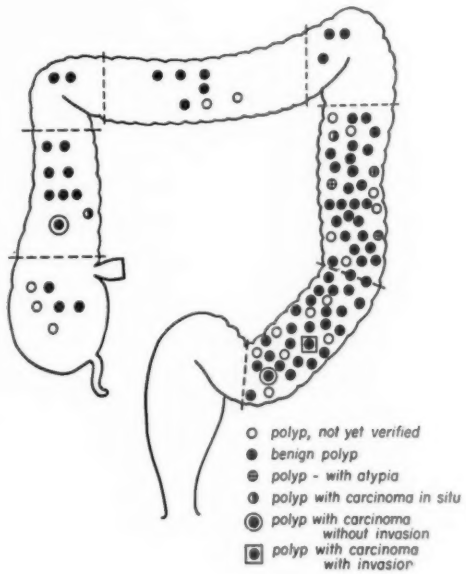
polyp, not yet verified
benign polyp
polyp - with atypia
polyp with carcinoma in situ
polyp with carcinoma without invasion
polyp with carcinoma with invasion

Fig. 2.

Fig. 1.—Distribution of polyps seen during proctosigmoidoscopy. Each dot represents 10 lesions.

Fig. 2.—Distribution and histology of polyps discovered by double-contrast enema examinations. Each circle represents one lesion.

TABLE I. RESULTS OF BIOPSY IN LESIONS VISIBLE THROUGH SIGMOIDOSCOPE

REPORT	NUMBER
Benign adenoma	384
Normal mucosa	34
Fibropapilloma	6
Chronic inflammation	5
Submucosal lymphoid tissue	2
Villous adenoma	3
Carcinoid tumor	3
Adenoma with atypia	2
Adenoma with malignant change, without invasion	3
Adenoma with malignant change, with invasion, or frank adenocarcinoma	12
Total	454

*The many lesions found in the 2 patients with multiple familial polyposis are excluded from these tabulations.

only the larger lesions because, with rare exception, tumors only 5 mm. in diameter and larger were biopsied. The diagnosis—"normal mucosa"—would probably not be used by many pathologists, who would prefer to call these areas mucosal hyperplasia or small mucosal excrescences.

Burnikel and Schutte[2] showed that the colonic area in which polyps are most frequently found is the area 14 cm. from the mucocutaneous junction on the posterior wall. The present study confirms their observation and indicates that a preponderant number of these lesions is found at the 13 to 14 cm. level. (See Table II.) Thirty-four per cent of all polyps seen by proctosigmoidoscopy in this study were in the posterior quadrant. Castro, Ault, and Smith[3] had also noted the higher incidence of polyps on the posterior wall between 3 and 5 inches from the anus.

TABLE II. LOCATION OF POLYPS SEEN AT PROCTOSIGMOIDOSCOPY

SITE (CM. FROM ANORECTAL MARGIN)	NUMBER
0-5	78
6-7	129
8-9	234
10-11	349
12-13	504
14-15	501
16-17	252
18-19	190
20-21	81
22-23	30
24-25	18

In Burnikel's study, about half of the lesions discovered were 1 to 3 mm. in diameter. Rider and co-workers,[11] in a study of asymptomatic patients, unselected for age, found that 16.7 per cent of all the lesions were less than 3 mm. in diameter. In the present series, nearly all of the lesions were under 5 mm. in diameter and about half were less than 3 mm. (See Table III.)

TABLE III. SIZE OF POLYPS SEEN AT PROCTOSIGMOIDOSCOPY

SIZE	NUMBER
Less than 3 mm.	1082
3 to 5 mm.	1055
6 to 10 mm.	166
11 to 15 mm.	33
16 to 20 mm.	11
Greater than 20 mm.	19
Total	2366

Of the 876 patients in whom polyps were found at the first examination, 639 (73 per cent) were found to have single lesions and the remaining 237 (27 per cent) were found to have 2 or more lesions in the area visualized by endoscopy. In the total experience (1,462 patients), 912 or 62 per cent were found to have a single lesion, and 540 (38 per cent) were found to have 2 or more lesions on one or more examinations. These are in keeping with the percentages of patients with single and multiple polyps reported by other authors.[2, 7, 13]

The male-female ratio of the total number of patients examined at the Center was 0.95 to 1. Among the 1,462 patients with polyps there were 892 men and 572 women, giving a male-female ratio of 1.56 to 1. This ratio is essentially the same as those reported by other authors[8, 9, 11] and is exactly the same as previously reported for patients with polyps at this Center.

These patients are selected by age; consequently, averages and other calculations concerning age are of less significance than in reports of unselected patients. We found the average age of the total number of patients and the average age of the patients with polyps to be essentially the same: 55.2 years and 55.5 years, respectively. Of the 7,608 patients examined, there were 3,966 (52 per cent) between the ages of 45 and 54, 2,977 (39 per cent) between the ages of 55 and 64, 615 (8 per cent) between the ages of 65 and 74, and 50 (0.6 per cent) over the age of 74. It was found that the incidence of polyps in the patients in these age groups was 18, 19.8, 25, and 20 per cent, respectively. It is interesting to note that the incidence of polyps in the patients over 74 years is no greater than in the patients in the 2 youngest decades studied here. Hauch and co-workers[7] noted a progressive rise in the incidence of polyps from the second through the eighth decades. It must be pointed out, however, that the number of patients over 74 years of age in this study is very small, and therefore the calculations concerning this group probably carry no statistical significance.

Because all of our patients were completely examined at each visit, a thorough documentation of abnormal findings involving other systems was available for reference. Therefore, an attempt was made to uncover any significant correlation between the incidence of polyps and the incidence of these other very common abnormalities. No significant correlation could be found between the incidence of polyps and the incidence of diverticulosis, diverticulitis, achlorhydria, hypochlorhydria, seborrheic keratoses, senile keratoses, nevi, lipomas, and leukoplakia.

In a very interesting and provocative paper, Diamond[5] showed that the incidence of polyps was much higher in mental patients confined for alcoholism than in mental patients confined for other reasons. Less than 3 per cent of the patients in the present study admitted to partaking even moderately of alcoholic beverages. It must be pointed out that the patient who volunteers to go through a Cancer Detection Center and who faithfully abides by all rules for preparation and for x-rays and other studies is not the "alcoholic type." It is probably true that the incidence of alcoholism is lower in this group of Detection Center patients than in the population at large.

There have been varying opinions expressed regarding the relationship of polyps to gross and occult bleeding per rectum. Certainly, it is difficult to believe that tiny adenomas, 3 mm. in diameter or smaller, can give rise to any symptoms, including bleeding. In our patients with rectal and sigmoidal polyps, the incidence of bleeding per rectum, gross or occult, is only 3.2 per cent, whereas in the entire group of patients examined the incidence of bleeding is 4 per cent. In an attempt to find out more accurately if the polyp was

the true source of bleeding, the incidence of bleeding was determined for polyp patients when the polyps were present and compared with the incidence of bleeding in these same patients when the polyps were removed or had disappeared spontaneously. It is interesting to note that the incidence of bleeding was less (1.7 per cent) when the polyps were present than when the polyps were absent (3.7 per cent). This is certainly strong suggestive evidence that polyps discovered by endoscopy are not the source of bleeding. The incidence of bleeding in patients with a polyp or polyps above the sigmoidoscoped area, however, (and these are larger polyps) is 12.5 per cent; bleeding per rectum in these patients might very well be assumed to be related to the polyp. Bacon[1] found the incidence of rectal bleeding in patients with colonic polyps to be 70 per cent, and DeMuth and associates,[4] 50 per cent; the discrepancy between their figures and the figure reported in this study can be attributed to the fact that they were dealing with symptomatic patients who were seeking treatment, while the patients in this study are presumably asymptomatic adults.

It was noted during the course of this study that many tiny adenomas disappeared without treatment. It is true that many of these lesions are so small that they may be seen by one examiner and missed by another. Therefore, the criterion used here for true disappearance of a lesion is the detection of the polyp by one examiner and then the failure of 2 or more examiners to locate the lesion again at successive annual follow-up examinations, the patient having had no treatment. A total of 93 polyps (in 79 patients) met this criterion. Most of these lesions were tiny; 57 were less than 3 mm. in diameter; 24 were 3 mm. in diameter; and 10 were 4 to 5 mm. in diameter. However, one lesion 8 mm. in diameter and another 40 mm. in diameter disappeared completely without treatment. During the same study period, 19 polyps in 18 patients were recorded as having shown signs of growth in the one or more years between examinations. In 2 patients, growth of the lesions was evident only after 3 years of observation. In one patient an untreated, unbiopsied, tiny lesion in the proctoscoped area grew until it was large enough to perform a biopsy upon and then proved to be malignant. This growth occurred over a 2-year period.

An attempt was made, using the data available from this study, to answer some of the many questions that are posed by the patient with a polyp or polyps in any part of the large bowel. For instance, if a patient has a polyp or polyps discovered by proctosigmoidoscopy, what are his chances of having a polyp or polyps discovered in the proximal colon by barium enema? From the results of this study, his chance is 4.5 per cent (3.7 per cent if there is a single lesion found by endoscopy, and 6.6 per cent if there are 2 or more lesions found by endoscopy).

If a patient has a polyp or polyps discovered by proctosigmoidoscopy, what are his chances of having a frank carcinoma discovered in the proximal colon by barium enema? From the results of this study, his chance is 0.34 per cent (5 cases).

If a patient has a polyp or polyps discovered by proctosigmoidoscopy, what are his chances of developing more polyps in the endoscoped area during the period of follow-up examinations? From the results of this study, his chance is 22 per cent (55 per cent of these patients developed a single additional lesion, and 45 per cent developed multiple additional lesions).

If a patient has a polyp or polyps discovered by proctosigmoidoscopy and they are completely destroyed, what are his chances of having one or more of these lesions recurring in the same site? From the results of this study, his chance is 2.7 per cent.

If a patient has a polyp or polyps discovered by barium enema examination and all of them are properly removed (polypectomy or segmental resection), what are his chances of developing another polyp in the colon not visualized by proctosigmoidoscopy? During the period of this study, 2 patients (6 per cent) revealed additional lesions at follow-up barium enema examinations.

If a patient has a polyp or polyps discovered by proctosigmoidoscopy and the original barium enema examination is negative, what are his chances of having a cancer or polyps discovered in subsequent barium enema examinations? One might ask this question in another way: What is the necessity for repeating the barium air study at the time of each annual follow-up visit if the x-ray has once been negative? Among the 1,462 patients in this study, there were 27 in whom a satisfactory barium enema study was reported as negative on one or more consecutive examinations, and subsequently showed a polyp or cancer in the colon. I am not in a position to decide whether routine annual barium air enemas are warranted in order to detect a polyp or carcinoma in 2 per cent of the patients. Perhaps biennial x-ray studies are sufficient; Swinton and Doane[12] have suggested that patients with polyps be followed at 2-year intervals.

If a patient has a polyp or polyps discovered by barium enema, what are his chances of having more polyps in the colon, not visualized by x-ray? In this study, 10 of the 48 patients (21 per cent) operated upon for colonic polyps were found to have more polyps at operation than were discovered by x-ray. However, it is true that many of the surgeons operating upon these patients made only a casual digital exploration of the colon, attempting to discover more lesions. Coloscopy at the time of operation was rarely used. Subtotal colectomy was done in 4 patients in whom x-ray examination had shown one polyp (3 patients) or 3 polyps (one patient). Additional polyps were found in the surgical specimen in 2 of these patients. Two patients with 2 polyps seen by x-ray were found to have only single lesions at the time of surgical exploration.

DISCUSSION

The high incidence of polyps previously reported for patients examined in this Cancer Detection Center[6] is substantiated by the present study. Whether or not each lesion discovered represents a possible source of malignant degeneration cannot possibly be answered, even though the statement

is often made that all of these adenomatous polyps and papillomas are truly precancerous lesions. It seems proper to point out that many of the tiny lesions seen during endoscopy disappeared without any treatment whatsoever. This phenomenon was observed much more frequently than the phenomenon of growth and malignant degeneration of a tiny untreated polyp. A very revealing study might possibly be carried out by some investigator, in which study some of the very tiny lesions could be observed but not treated. In this way the true fate of the majority of these lesions might be learned. I believe that the risk is not as great as many believe. No such policy was even considered at the Cancer Detection Center, so that complete removal, with or without preliminary biopsy, is recommended for every lesion, no matter how small. The incidence of malignancy in the biopsied lesions discovered by proctosigmoidoscopy in this study was about 1 per cent. However, this incidence pertains to larger lesions only, and it has been shown that the incidence of malignancy definitely increases with the size of the polyps.[6] Therefore, the incidence of malignancy in the tiny lesions must certainly be less than 0.5 per cent. Two patients (about 0.5 per cent) of the patients treated for benign polyps died during that treatment. It would seem permissible therefore to consider a program of observation for the tiny lesions (less than 4 mm.) discovered at endoscopy.

The proper surgical management of colonic polyps discovered by x-ray is a much debated and, therefore, an unanswered problem. Twenty-one per cent of the patients in this study subjected to operation for colonic polyps were found to have more polyps in the colon than were discovered by x-ray studies, which were done very carefully and precisely. One can assume that if routine subtotal colectomy had been done the incidence of multiple lesions (most patients were operated upon for a solitary lesion found by x-ray) would be as high or higher than the 38 per cent found by Lillehei and Wangensteen.[10] Does this justify routine subtotal colectomy? I am beginning to believe so, for I have observed firsthand many of the patients operated upon by Wangensteen and also several operated upon by Teicher and Abrahams,[14] and I am convinced that the operative procedure is nearly as easily done as segmental resection, and the early and late morbidity is no worse than following the lesser procedure. If the operation is done properly, diarrhea is not a problem.

If all colonic polyps 5 mm. in size and larger are precancerous and will become malignant within a time interval pertinent to this discussion, that is, 5 to 10 years, there seems no question but that subtotal colectomy is indicated for every polyp or cancer discovered in the colon. Since we do not know if all polyps are truly precancerous or if so whether they will become cancers during the lifetime of the patient, there is logical room for argument about routine subtotal colectomy. Time will be the arbiter.

SUMMARY

1. The incidence of rectal and colonic polyps in 7,608 asymptomatic persons, 45 years of age and older, studied at the Cancer Detection Center at the University of Minnesota, is 19.2 per cent.

2. Associated symptoms and findings are recorded, and their possible significance is discussed.

3. The results of this study do not permit definite conclusions regarding the proper handling of rectal and colonic polyps.

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CANCER OF THE BREAST

A Comparison of Two Methods of Treatment

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EVEN a casual perusal of the literature emphasizes the fact that the correct treatment of breast cancer is a very debatable matter. Opinions vary from the untenable one that treatment has no effect[2, 7] to extended radical[8-10] through more orthodox standard radicals and the thesis of a simple mastectomy plus irradiation.[5, 6]

Prognosis in breast cancer is influenced by two sets of factors: (a) uncontrollable and (b) controllable. The, as yet, uncontrollable factors include: (1) age of patient, (2) inheritance, (3) location of tumor, (4) endocrine status of patient (this is partially controllable), (5) biologic activity of tumor, and (6) host resistance. The controllable factors are: (1) delay in treatment and (2) type of treatment. Early diagnosis and treatment do seem to favorably influence the prognosis.[1, 3] The main difference of opinion revolves about whether the type of treatment influences the outcome in breast cancer.

At the Confederate Memorial Medical Center (formerly Shreveport Charity Hospital), a unique opportunity presented itself to study the influence of treatment on prognosis. From 1931 to 1939 it was the policy of the Tumor Clinic to electively treat breast cancer with irradiation, followed by simple mastectomy.* Since 1940, the elective treatment has been a Willy Meyer type of radical mastectomy, when there were no contraindications.

During the first period (1931 to 1939) there were 216 cases of breast cancer in all stages seen. During the second period (1940 to 1951) there were 369 cases in all stages. Eliminating clinical Stage III cases in both groups left 98 in the first group (1931 to 1939) which were clinical Stages I and II treated with x-ray and simple mastectomy and 189 stages I and II in the second group (1940 to 1951) treated with radical mastectomy. (Table I.)

In group I (1931 to 1939) the absolute 5-year survival rate in Stages I and II cases was 22.4 per cent, corrected† to a 5-year survival rate of 33.8 per cent. In group II (1940 to 1951) the absolute 5-year survival rate in Stages I and II cases was 39.6 per cent, corrected to a 5-year survival rate of 60.5 per cent.

When the cases were divided into clinical Stage I and Stage II, it was found that in group I the absolute 5-year survival of the Stage I cases was

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*This differs from McWhirter's recommended procedure of simple mastectomy followed by irradiation. The irradiation given was usually with filter 0.5 mm. Cu. and 1.0 mm., and a total of 1100 r. which is considerably less than McWhirter has used.

†Statistics were "corrected" by eliminating cases lost to follow-up, cases dead from any cause other than cancer of the breast, and cases living when last seen but who at the time of tabulation had not survived 5 years.

TABLE I

	1931-1939				1940-1951			
	TOTAL NO. CASES (ALL STAGES)	TREATED WITH X-RAY AND SURGERY		CASES TREATED BY OTHER METHODS (ALL STAGES)	TOTAL NO. CASES (ALL STAGES)	STAGE I	STAGE II	CASES TREATED BY OTHER METHODS (ALL STAGES)
		STAGE I	STAGE II					
5-year survivors	43	16	6	21	100	57	18	25
Living when last seen but not 5-year survivors	0	0	0	0	9	6	2	1
Lost due to follow-up	24	13	2	9	72	14	24	34
Dead due to cancer of breast	120	23	20	77	150	18	31	101
Dead due to causes other than breast cancer	29	11	7	11	38	9	10	10
Total cases	216	63	35	118	369	104	85	180
Absolute 5-year survival rate	19.9%	23.8%	17.1%	17.8%	27.1%	54.8%	21.2%	13.9%
Corrected 5-year survival rate	26.4%	41%	23.1%	42.9%	40.0%	76.0%	36.7%	19.8%

23.8 per cent, corrected to 41 per cent, while in the second group the absolute 5-year survival rate of Stage I was 54.8 per cent, corrected to 76 per cent. In the Stage II cases, the absolute 5-year survival in group I was 17.1 per cent, corrected to 23.1 per cent, while in group II the absolute 5-year survival rate was 21.2 per cent, corrected to 36.7 per cent.

Local recurrence has generally been accepted as an indication of failure of the primary purpose of the operation of radical mastectomy, namely, elimination of local disease. In these combined series, there was a total of 207 radical mastectomies done; 5 were done in the first period and 202 in the second period. Local recurrence occurred in 22 cases or 10.9 per cent. This compares favorably with other reported series,[4] indicating we have not had an unusually high local recurrence rate and that a technically adequate radical mastectomy was being done. (Table II.)

TABLE II. THE RADICAL MASTECTOMY IN THIS HOSPITAL

GROUP	NUMBER
1931-1939	5
1940-1951	202
Total	207

Local recurrence occurred in 22 cases. This represents technical failure in 10.9 per cent of the cases done.

An interesting corollary of this study was a comparison of biopsy methods and survival rates in patients treated with radical mastectomy. Excisional biopsy was followed by 73.9 per cent absolute 5-year survival (corrected to 85 per cent), followed by frozen section with a 39.5 per cent absolute 5-year survival rate (corrected to 68.2 per cent). This was closely followed by aspiration biopsy, which had an absolute survival rate of 35.2 per cent (corrected to 50 per cent). Pinch biopsy was followed by a 20 per cent absolute survival rate (corrected to 28 per cent) and incisional biopsy was followed by a 20 per cent absolute 5-survival rate (corrected to 25 per cent). It is assumed that

TABLE III. THE RELATIONSHIP OF SURVIVAL TO METHOD OF BIOPSY IN PATIENTS WITH CARCINOMA OF BREAST TREATED WITH RADICAL MASTECTOMY

	FROZEN	EXCISION	ASPIRATION	PINCH	INCISIONAL	OTHER	TOTAL
Total 5-year survival	15	17	32	2	1	10	77
Living when last seen but not 5-year survival	5	0	3	0	1	0	9
Lost to follow-up	6	2	15	3	0	16	42
Dead due to carcinoma	7	3	32	5	3	8	58
Dead due to causes other than breast carcinoma	5	1	9	0	0	6	21
Total	38	23	91	10	5	40	207
Absolute	39.5%	73.9%	35.2%	20%	20%	25%	37.2%
Corrected	68.2%	85%	50%	28.6%	25%	55.6%	52%

the method of biopsy is largely influenced by the size and location of the tumor and it is these factors that influence prognosis rather than the actual method of biopsy used. The better results following excisional biopsy, for example, probably represent a smaller and earlier primary lesion lending itself to complete excision.

SUMMARY AND CONCLUSIONS

1. A statistical study of breast cancer treated by two different methods at Confederate Memorial Medical Center is presented.

2. In the first period (1931 to 1939) there were 98 cases of clinical Stages I and II breast cancer in which treatment was irradiation followed by a simple mastectomy.

3. In the second period (1940 to 1951) there were 189 cases of clinical Stages I and II breast cancer treated with radical mastectomy.

4. The absolute survival rate in the first period (Stages I and II) was 22.4 per cent; in the second period, this absolute survival rate was 39.6 per cent.

5. Corrected survival rates in Stages I and II in the period 1931 to 1939 was 33.8 per cent, while the corrected survival rate in the period 1940 to 1951 was 60.5 per cent.

6. The absolute 5-year survival rate in Stage I cases in the first period (1931 to 1939) was 23.8 per cent (corrected to 41 per cent) as compared to an absolute 5-year survival rate in the second period of 54.8 per cent (corrected to 76 per cent).

7. The absolute 5-year survival rate in Stage II cases in the first period was 17.1 per cent (corrected to 23.1 per cent) as compared to an absolute 5-year survival in the second period of 21.2 per cent (corrected to 35.7 per cent).

8. In clinical Stages I and II the 5-year survival rate following radical mastectomy was almost twice that of similar cases treated by irradiation and simple mastectomy in this institution.

9. A total of 207 radical mastectomies was done in both series with a local recurrence rate of 10.9 per cent.

10. The higher 5-year survival following excisional biopsy prior to radical mastectomy probably reflects a smaller and earlier primary lesion lending itself more readily to complete excision.

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THE USE OF A GASTRIC TUBE TO REPLACE THE ESOPHAGUS AS PERFORMED BY DR. DAN GAVRILIU OF BUCHAREST, RUMANIA

A Preliminary Report Following a Visit to Bucharest, Rumania

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INTRODUCTION

IN THE April, 1955, issue of Surgery, Dr. James Winfield and I described a one-stage procedure whereby a tube created from the greater curvature of the stomach is utilized to by-pass or replace the esophagus. A historical review describing the development of this procedure was included in the paper.[1] To this should be added the experimental work of Swenson and Magruder.[5]

An abstract of this paper was published in *Surgery, Gynecology and Obstetrics,* in October, 1955.[2] Shortly thereafter, a letter addressed to Dr. Alton Ochsner, Editor of Surgery, from Dr. Dan Gavriliu of Bucharest, Rumania, was forwarded to Dr. Winfield and I. Dr. Gavriliu, in this letter, stated that he had performed this operation successfully in 50 patients since April 20, 1951, and that his results had been published in Rumanian medical journals. A search for Dr. Gavriliu's references in the Library of the New York Academy of Medicine revealed that the journals had not been received in the United States for 10 years and were not included in any American index for that period.

In subsequent letters, Dr. Gavriliu enclosed copies of the Rumanian publications in which his papers on the gastric tube appeared and a review of his more recent work on that subject. On the basis of this material the gastric tube operation appeared to have great merit. The Rumanian Academy of Science thereafter extended an invitation to Dr. Winfield and I to visit Rumania. I travelled to Bucharest, arriving on Sept. 25, 1956, and remaining until Oct. 3, 1956. The observations made in Rumania are the basis of this report.

The following preliminary report on the work of Dr. Gavriliu is submitted in order that the procedure may become known to American surgeons and that Dr. Dan Gavriliu be given priority in having described and successfully performed an operation utilizing a reversed tube created from the greater curvature of the stomach to replace the esophagus.

PRELIMINARY REPORT

Dr. Gavriliu's procedure for replacing the esophagus is similar to that which was described experimentally by Dr. Winfield and I.[1] A tube is created

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from the greater curvature of the stomach, retaining its attachment at the cardia. The left gastroepiploic vessels are preserved to maintain the vascular supply to the tube. The spleen is resected to give greater length to the left gastroepiploic vessels and to the gastric tube. The tube is reversed and the antral end is brought to the neck either subcutaneously, retrosternally, or intrathoracically and is easily anastomosed to the pharynx or cervical esophagus. The remainder of the stomach remains in its normal position in the abdomen and retains its storage function.

Dr. Gavriliu has perfected the operation by freeing the pancreas from its bed in order to give the gastric tube greater length. His procedure differs from ours in that Dr. Gavriliu prefers to place the gastric tube in a subcutaneous, presternal position rather than within the chest. However, Dr. Gavriliu has successfully used both methods.

The first successful gastric tube operation was performed by Dr. Gavriliu on April 20, 1951, a report of which appeared in a Rumanian medical journal 2 months later.[3] He demonstrated his first 17 successful cases, in 1952, to the Rumanian Society of Surgery. In May, 1955, he published the results of the gastric tube operation in 40 patients.[4]

Dr. Gavriliu has now performed 52 operations for benign and malignant stricture of the esophagus. The ages of the patients range from 4 to 65 years. Ten patients had had unsuccessful previous surgical intervention including skin tubes and jejunal and colic transplants. The gastric tube procedure was successful in restoring esophagogastric continuity in all these cases. Five patients developed small fistulas at the anastomotic site and narrowing at the anastomosis. A secondary procedure cured this complication in 4 of these patients.

Of the 52 patients, 4 suffered from carcinoma of the cervical esophagus which spread into the larynx and to the cervical lymph nodes. At operation, the esophagus and larynx were excised and bilateral radical neck dissection was performed with preservation of one internal jugular vein. At a second stage, the gastric tube procedure was successfully performed by Dr. Gavriliu. The anastomosis in these patients was made between the gastric tube and the pharynx after resection of the hyoid bone. An anastomosis at this level was also performed in some patients with high benign strictures. The majority of patients, however, had anastomoses at the level of the cervical esophagus. I examined 2 patients who had had radical resections for carcinoma of the cervical esophagus with extension as described above. One of these patients was operated upon 3½ years ago; the other, one year ago. There was no evidence of recurrence of the tumor and the patients were able to swallow all foods in a normal manner. One of the patients had developed a well-functioning esophageal voice through the gastric tube.

Dr. Gavriliu has had no operative mortality in performing the gastric tube procedure. One patient with a benign stricture committed suicide several weeks after surgery by swallowing a greater amount of lye than he had been able to swallow at the first attempt.

During my stay in Bucharest, 2 gastric tube procedures were performed for me by Dr. Gavriliu. I assisted at both operations and motion pictures were made of the procedure for me. The ease with which the procedure was accomplished was impressive, when performed by 2 teams.

The operation should take no longer than 3 or 3½ hours. Resection of the lesion can be performed as a preliminary or secondary procedure, if necessary. The gastric tube, which need be only 1.5 to 2 cm. in diameter to function adequately, is barely visible under the skin. At least four-fifths of the stomach remains in the abdomen and retains its normal storage function. Peptic esophagitis does not occur for the reason that the proximal esophagus is anastomosed to the nonacid secreting antral mucosa. The entire esophagus can be resected from the pharynx to the cardia of the stomach.

One gastric tube operation was performed on the day after my arrival in Bucharest. The patient was seen to swallow a full glass of water without difficulty on the fifth postoperative day. Several patients who had been operated upon several months to years previously were examined and fluoroscopy with a barium swallow was performed. The gastric tube in these patients was seen to have developed isoperistaltic waves which were visible on fluoroscopy, and a sphincter-like action was present in some patients at the site where the tube crossed the costal margin.

I believe that the procedure of Dr. Dan Gavriliu is of great value in overcoming the problem of esophageal replacement, particularly for carcinomatous and benign lesions of the upper and middle thirds of the esophagus. Dr. Gavriliu's contribution in the field of esophageal surgery is, without doubt, a most worthy one.

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ADDENDUM

Dr. Winfield and I performed a successful reversed gastric tube procedure using the method of Gavriliu, on April 20, 1957, at the Metropolitan Hospital Center of The New York Medical College. The distal end of the cervical esophagus was closed and the antral end of the gastric tube was anastomosed to the cervical esophagus 2 cm. from the pharynx. The patient, a 59-year-old man with inoperable carcinoma of the upper and middle thirds of the espohagus, has been able to eat a solid diet and has gained weight to the present time (July 16, 1957).

LIPOMAS OF THE HAND

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LIPOMAS are common tumors, but the number which has been reported in the hand is exceedingly small. Adair, Pack, and Farrior[1] in 1932 reported 352 lipomas occurring in 134 patients. They found only 2 lipomas of the hand, both on the dorsum. Straus,[11] in reporting a deep lipoma of the hand in 1931, called attention to its rarity and to the almost constant errors in their preoperative diagnosis. Pack,[8] in a symposium listing 204 benign tumors of the hands and feet, found only 4 lipomas of the hand in the entire group. Mason[7] said that lipomas are not frequently found in the hand but illustrated 3 cases in his report. The specimen of one of them, otherwise unreported, was through the courtesy of another surgeon. Aldredge and Halpert[2] in 1948 reported a lipoma of the thenar eminence and said that their case was the eleventh palmar lipoma reported. Only 3 subsequent reports have appeared in the literature.[3, 5, 6] All 3 deal with single instances of lipomas of the palm.

We wish to present a series of 4 cases of lipoma of the hand, 3 of which were in the palm and one of which was on a finger. Thus we bring the total of palmar lipomas to 17. It is difficult to appraise the total number of lipomas of the finger because such tumors are usually discussed without specific references.

CASE REPORTS

CASE 1.—E. D., a 44-year-old woman, who was seen in June, 1941, complained of a mass which had been present in the palm of her right hand for one year. Beginning in the midpalm, it enlarged to encroach on the web space between the second and third digits. Numbness developed in the palm and in the palmar surface of the first 3 digits. There was no history of inflammation. Physical examination disclosed no obesity and was normal except for the findings in the right hand (Fig. 1, *A*). The preoperative diagnosis was lipoma.

On Aug. 18, 1942, with the patient under general anesthesia and with a tourniquet inflated, an incision was made in the distal flexion crease of the palm. Division of the palmar fascia exposed a tumor with the gross characteristics of a lipoma. The tumor extended distally over the second and third metacarpal bones and compressed the digital nerves of the corresponding lumbrical canals. The location of the tumor appeared to explain the numbness. The tumor was completely removed, the wound was closed in layers, and a pressure dressing and a splint were applied. The specimen consisted of an oblong mass of soft, yellow-gray tissue measuring 4.5 by 2 by 0.5 cm. It was invested in a transparent fibrous capsule. The microscopic diagnosis was lipoma. The postoperative course was uneventful, recovery was prompt, and normal sensation returned in 4 to 5 weeks (Fig. 1, *B*).

CASE 2.—B. J., a 63-year-old painter, was admitted to Mercy Hospital on March 24, 1942, because of a painless swelling of the thenar region of his right hand (Fig. 2). It had first appeared at the base of his thumb a year before. As it had grown to the size illustrated,

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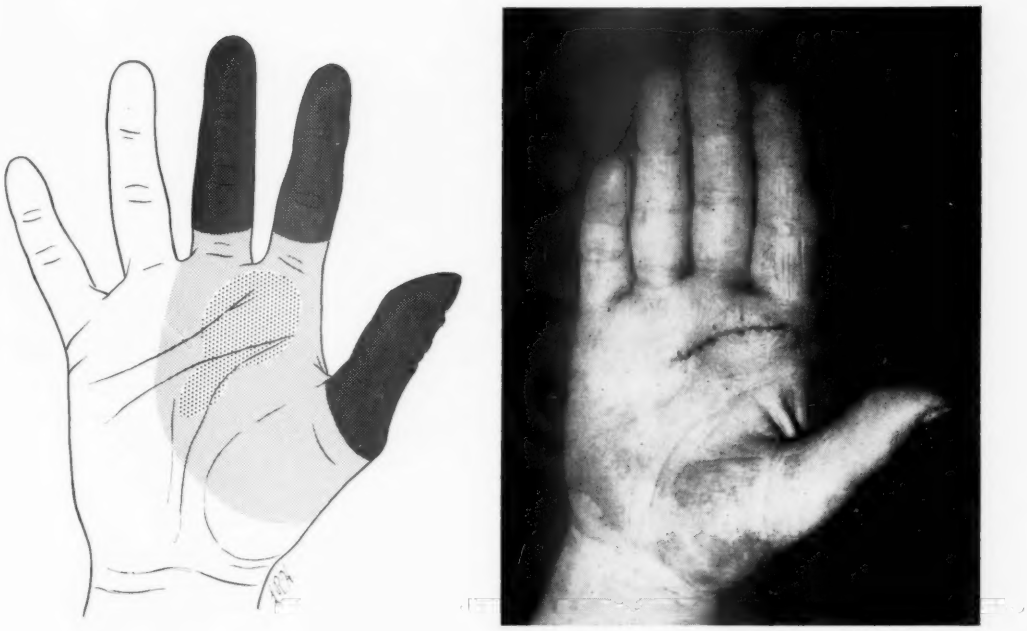

A. *B.*

Fig. 1.—*A*, Diagrammatic presentation of findings in Case 1. The stippled area outlines the site and extent of the lipoma. Severe numbness is indicated by the dark shading, mild numbness by the light shading. *B*, Healing incision in Case 1. Numbness began to decrease within 2 weeks after surgical removal of palmar lipoma.

Fig. 2.—Prominence of the right thenar region due to palmar lipoma in Case 2.

it had led to mechanical impairment of function. The patient was otherwise asymptomatic, and the soft fluctuant mass was the only significant finding. A roentgenogram disclosed no abnormality in the bones of the hand. The preoperative diagnosis was ganglion involving the sheath of the long flexor tendon of the thumb. On March 25, 1942, with the patient under general anesthesia and with a tourniquet inflated, an incision was made over the

A.

B.

Fig. 3.—*A*, Lipoma of the hypothenar eminence in Case 3. Note that it extends proximally to the region of the transverse carpal ligament. *B*, Palmar lipoma excised in Case 3. Note the partial division of the specimen into 3 blunt projections leading to the corresponding lumbrical canals.

thenar eminence. The abductor and flexor pollicis muscles were separated to expose the mass, which had the gross characteristics of a lipoma. The only point of attachment appeared to be in the region of the first metacarpal bone. The tumor was removed, the wound was closed in layers, and a pressure dressing and a splint were applied.

The specimen consisted of a roughly oval mass composed of lobulated, greasy, orange-yellow tissue which was invested by a thin, glistening, reddish-gray capsule. It measured 4.9 by 4.2 by 2.6 cm. The microscopic diagnosis was lipoma. The postoperative course was uneventful except for a transient numbness of the palmar surface of the distal phalanx of the thumb. Recovery was complete at the time of an out-patient visit one month later.

CASE 3.—E. D., a 27-year-old Negro housewife, had had a swelling in the hypothenar region of the right palm since childhood. It had recently become tender. The only significant physical finding was a mass in the hypothenar region extending from the long crease of the right palm to the ulnar edge of the hypothenar eminence and from the flexion crease of the wrist to the distal flexion crease of the palm (Fig. 3, *A*). The mass was soft and fluctuant. Since pressure on the mass produced a bulge in the wrist, we suspected the mass of extending beneath the transverse carpal ligament. The preoperative diagnosis was ganglion or ulnar bursitis.

On Sept. 7, 1949, a mid-palmar incision was made and curved into the distal flexion crease medially. The flap of skin and subcutaneous tissue was reflected. Portions of a tumor having the gross characteristics of a lipoma were seen protruding through the interstices of the palmar aponeurosis. The aponeurosis was divided longitudinally and the tumor was found to lie upon the flexor tendons. It extended beneath the carpal ligament. It was removed uneventfully. The wound was drained by a strip of rubber and closed in layers. A pressure dressing was applied. The specimen was a yellow lobulated mass measuring 6.5 by 6 by 2 cm. (Fig. 3, *B*). The microscopic diagnosis was lipoma. Complete recovery ensued.

CASE 4.—M. M., a 30-year-old white housewife, had a swelling in the mid-portion of her right index finger which had slowly increased in size since its inception more than 5 years earlier. There was no pain or tenderness. Physical examination showed a cystic swelling of the middle phalanx of the right index finger involving both the dorsal and ventral aspects. The preoperative diagnosis was ganglion.

On July 6, 1955, the volar prominence of the mass was exposed through a longitudinal incision. It had the gross appearance of a lipoma and extended dorsally on the radial side of the phalanx to connect with a similar mass on the dorsum by a narrow isthmus. A separate dorsal incision was made to permit removing the dorsal mass after the connecting segment had been divided. The wounds were closed, and pressure dressings were applied. The specimen consisted of soft, yellow, fatty tissue. The total mass measured 3 by 2 by 0.5 cm. The microscopic diagnosis was lipoma.

DISCUSSION

Reports of lipomas of the hand repeatedly emphasize the problems in the preoperative diagnosis. The disability caused by a lesion occupying space in the close confines of the hand is usually sufficient cause for surgical excision. The difficulties in the preoperative diagnosis of soft tissue lesions of the hand make surgical exploration necessary for diagnosis in most instances. The fact that lipomas of the hand are fluctuant probably accounts for the erroneous diagnosis of cystic conditions, such as ganglia, which is made in many instances. It is likewise the reason for diagnosing tuberculous tenosynovitis when a soft lipoma extends along a tendon sheath and reaches the region of the carpal ligament as in Case 3.

Another factor in the high percentage of cases incorrectly diagnosed before operation is their rarity. Few surgeons have encountered a lipoma of the hand, and of course fewer have seen more than one. Nevertheless, the lesion in our

first patient was diagnosed correctly, whereas the lesion in our second patient, seen about a year later, was incorrectly diagnosed as a ganglion because of the soft fluctuation.

Sensory changes in fingers and palm because of pressure on nerves is often a significant finding in palmar lipoma, as Mason has emphasized. This finding might distinguish the lesion if the same thing did not occur in certain types of ganglia, as reported by Seddon.[10] We have not applied cold, which makes a lipoma become firm, as mentioned by Bunnell[4] and by Posch.[9]

The ramifications of a lipoma anywhere in the body can be both extensive and surprising, particularly when they occur in the region of a joint. In the hand a lipoma may extend from the palmar to the dorsal surface or along the course of tendons or lumbrical canals. Mason[7] has called attention to the difficult problem of complete extirpation of some of these lipomas. Obviously we believe that preparations for a major surgical procedure should be made when a palmar lipoma is to be excised. General anesthesia or brachial plexus block is necessary. A bloodless field must be provided for careful dissection in the complicated anatomy of the palm. Nerves, tendon sheaths, tendons, and vascular structures must be seen clearly to avoid damage to them. Hemostasis must be complete before the wound is closed. Finally the skillful use of pressure dressings and suitable immobilization during the initial period of healing are urgently recommended. If extirpation is complete there should be no recurrences.

SUMMARY

1. A report of 4 lipomas of the hand is made; 3 were in the palm of the right hand and one was in a finger.

2. The rarity of lipomas of the hand is emphasized as are the difficulties in diagnosis. Only occasionally has the correct diagnosis been made prior to operation. It was made in one of our 4 cases.

3. Unhurried careful dissection in a bloodless field is necessary for complete uncomplicated removal.

4. Our cases bring the total of recorded palmar lipomas to 17. We have been unable to determine the total number of reported lipomas of the finger.

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PROLONGED MASSAGE OF THE FIBRILLATING HEART

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A MAJOR catastrophe that occurs, particularly during surgery near the heart, is fibrillation of the heart.[7] Although many hospitals now have defibrillation equipment, a considerable lapse of time may occur if this equipment is not instantly available, and, therefore, the heart must be massaged until proper preparations are made. The purpose of massage is to maintain circulation to the cerebral tissue to prevent cerebral damage.[5] The intention of this study was to determine if, by maintaining the arterial blood pressure at a higher level than that obtainable by massage alone, prolonged massage could be affected without damage to the central nervous system. It soon became apparent, however, that some factor other than cerebral damage must be considered. The following are the results of this study with some comments on the mechanism that appeared to be active in producing death of the animals.

METHODS

Healthy dogs were anesthetized with 30 mg. per kilogram of sodium pentobarbital. An endotracheal catheter was placed for artificial respiration and the femoral artery was cannulated for arterial pressure measurements. The chest was opened on the left side and the heart exposed. The heart was then fibrillated and immediate massage of the heart began, using powder puff sponges backed by plexiglass to decrease damage to the heart. Two periods of time were selected, 30 minutes and 60 minutes. In some of the animals an intravenous drip of Locke's solution containing epinephrine, 3 mg. per 100 c.c. of solution, was given at a rate such that the arterial blood pressure was maintained above 70 mm. Hg. Other animals were subjected to the same periods of time without this aid to increase pressure. At the end of the designated period of time, the heart was defibrillated, if possible, and the chest closed. Blood pressure was recorded in many instances for several hours after closure of the chest.

RESULTS

Thirty Minutes of Cardiac Massage With Epinephrine.—A total of 9 dogs were subjected to 30 minutes of cardiac massage. At the end of the 30-minute periods, 2 of the animals could not be defibrillated. The remaining 7, however, were defibrillated and in most instances the blood pressure returned to

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the normal or control level. However, the blood pressure slowly declined, and all of the animals died, living an average of 8 hours with a range of 1 to 21 hours.

Thirty Minutes of Cardiac Massage Without Epinephrine.—Four dogs were subjected to 30 minutes of cardiac massage without the previously mentioned aid in maintaining blood pressure. The blood pressure in these dogs slowly decreased as massage continued, and at the end of the 30-minute period was frequently no more than 30 to 40 mm. Hg. These animals were defibrillated and their blood pressure rose within a few minutes to normal and all 4 survived permanently with no cerebral damage or other obvious defects.

Sixty Minutes of Cardiac Massage With Epinephrine.—A total of 14 dogs were subjected to 60 minutes of cardiac massage. At the end of this time, 3 of the hearts could not be defibrillated because of tracheal obstruction due to hemorrhage. Of the remaining 11, all were defibrillated. However, the arterial pressure usually did not rise to control levels and slowly declined. The dogs lived for an average of 4½ hours with a range of 2 to 12 hours.

Sixty Minutes of Cardiac Massage Without Epinephrine.—Two dogs were subjected to 60 minutes of cardiac massage, and the blood pressure as maintained by massage was usually between 20 and 30 mm. Hg during most of the time of massage. Yet, at the end of the period, the hearts were defibrillated, the pressure rose to normal, and both dogs survived.

DISCUSSION

It would appear that the use of epinephrine to maintain a high arterial pressure would supply the cerebral tissues with a greater blood flow than that resulting from massage alone since the cerebral arteries are not markedly constricted by epinephrine, and thus, with this adequate supply of blood, massage could be continued for a long time, the heart could be defibrillated, and the animal should live. However, the results indicate that survival is more likely to occur if the epinephrine is not given. Perhaps the reason for this is due to the development of irreversible shock. It may be recalled that if an animal is bled until his arterial pressure is 30 mm. Hg, and this condition is maintained for a period of time, then the animal will develop irreversible shock and die.[8] It is also known that large quantities of epinephrine will occasionally cause the development of irreversible shock, especially if the animal has previously lost some of his blood.[1, 4] That appears to be the cause of death in these animals in which the blood pressure was maintained at a high level. Under the conditions, it seems that the cerebral blood flow would be maintained at a sufficient level to prevent damage to the nervous tissue. However, this probably caused a great decrease in blood flow to the remaining tissues, and the epinephrine caused a great increase in their metabolic rate. Thus, in these animals with a low cardiac output, there was developed a normovolemic hypotensive shock aggravated in particular by the injection of epinephrine. A

unique feature of producing shock in this manner is that the animal cannot die when the shock becomes severe enough to cause death of an animal with a circulation maintained by the normal action of the heart. It also appears that irreversible shock will occur if the duration of hypotension is long enough even in animals not given epinephrine.

One of the especially noted features about the animals treated with epinephrine is that within a period of time varying from 15 minutes up, the blood developed a prolonged coagulation time which progressed into noncoagulable blood, or if coagulation did occur, only a small portion of the blood in the withdrawn sample would clot. Thus, despite the fact that these animals were defibrillated successfully, bleeding then became profuse, and it was not possible to control this bleeding by the injection of either protamine sulfate or toluidine blue. However, whole blood was sometimes effective in controlling the hemorrhage. The animals died, however, whether or not the hemorrhage was controlled. The cause of this profuse hemorrhage was not studied under the condition of prolonged massage since vigorous agitation of the blood would obviously question any results obtained. However, once it became evident that the dogs treated with epinephrine would not survive whereas those that were not treated would survive, the bleeding phenomena was then studied under conditions of hemorrhage which normally produce shock.[3] The data derived from recent experiments indicate that what may have been happening to these dogs is as follows:

At best, cardiac massage is a poor substitute for the normal action of the heart. Therefore, the cardiac output is greatly decreased. Under this condition, it appears likely that the supply of oxygen to the tissues is decreased, and this would result in the accumulation of metabolic end products from anaerobic metabolism which are acid in nature, particularly lactic acid. The effect of this acidification of the tissues would result in acidification of the blood in the adjacent capillaries, and thus, the blood becomes acid and the blood protein hemoglobin, pI = 6.8, would become insoluble, a condition somewhat similar to that occurring in the kidney tubules following the injection of incompatible blood.[6] It is believed that this occurred in these animals causing the cohesion of erythrocytes and the eventual formation of fibrin clots. Thus, the coagulation mechanism was profoundly disturbed, and the emboli and thrombi spread throughout the circulatory system, resulting in general decay. The final result was death of the animal. The ultimate proof of this theory will require extensive experimentation. However, some portions of it have been completed and seem to indicate that it may be true.[2, 3]

Thus, when fibrillation occurs and massage is instituted within a short time, it is not damage to the central nervous system that is of immediate concern. It is the development of irreversible shock, and this can be prevented by restoring the circulation to its normal state.

SUMMARY

Animals have been subjected to long periods of cardiac massage following fibrillation of the heart. Commensurate experiments indicate that if epinephrine is injected, the heart has a better tone, massage is more effective, and the blood pressure is higher. Yet, the likelihood of survival is decreased because of the development of shock.

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FROZEN IRRADIATED HETEROGRAFTS

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INTRODUCTION

WITH the transplantation of arterial homografts in vascular diseases now a successful and established treatment, one of the great obstacles faced by the surgeon is the difficulty in procurement of suitable homologous vessels. Attempts to solve this problem have been made by investigators experimenting with the development of artificial prostheses of plastics and with the use of heterografts. An experience with heterografts is the subject of this paper.

Vessels of animal origin are available in an unending supply, but their use in human beings has had limited application.[9, 11] Study in the use of heterologous arterial and venous grafts in experimental animals has shown that our knowledge of their preparation and of their reactions to the host tissues is not yet adequate to justify their use. Although occasional success has been obtained with this type of graft in the past, no sure method of procurement or preparation has been found which consistently gives good results.

Carrel[1, 2] reports varying degrees of success in a small series of dog-to-cat and human-to-dog heterografts. Guthrie[5, 6] likewise had some success with rabbit-to-dog and cat-to-dog transplants. The methods of preservation used were normal saline, defibrinated dog blood, Locke's solution (all at 32 to 34° F.) smearing with petroleum jelly, and 2.5 per cent formalin.

The method of preservation by Gross, Bill, and Peiree[4] was modified Tyrode's solution plus 10 per cent dog serum, refrigerated at 1 to 4° C. They realized some degree of success with hog and human-to-dog transplants for a protracted period of time; however, degeneration with dilatation eventually occurred. The combination of baboon-to-dog transplants was a complete failure.

Creech, DeBakey, Halpert, and Self[3] employed a penicillin and streptomycin sterilized freeze-dried method and a 4 per cent neutral formalin preserved method of hog-to-dog transplants. The results, for the most part, were without success and showed no choice between the two types of preservation. Hufnagel[9] utilized in dogs heterografts sterilized with liquid ethylene oxide and preserved by freeze-drying methods, which have also given excellent results with human, calf, and hog donors. He attributes this success to the fact that the ethylene oxide does not alter the tissue, thereby rendering it thrombogenic. Morten and

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Mahoney,[14] using hog-to-dog heterografts stored in 3° C. Ringer's solution containing penicillin, found that even though the grafts were wrapped with polyvinyl formal sponge, aneurysmal dilatation occurred in all grafts that remained patent long enough for degenerative changes.

Kimoto[11] reports using 70 per cent ethyl alcohol and pure ethyl alcohol for the preservation of human vessels transplanted into dog aortas. Alcohol-preserved vessels were definitely superior to the fresh viable graft preserved in Ringer's solution plus 10 per cent donor's serum. This led him to utilize 70 per cent ethyl alcohol-preserved heterografts clinically with similar results, although the follow-up period (25 days or less) is limited. The rationale in the use of alcohol in the preservative was based on the presumption that chemical denaturization of the protein fraction and the dissolution of lipoproteins would reduce antigenic potentialities.

A similar degree of success has been reported by Hardin[7] in the use of human, pig, cat, monkey, and goat-to-dog transplants, freeze preserved with ethyl ether and solid CO_2. Cat, monkey, and goat vessels were complete failures, but the author felt encouraged by a few successful human and hog vessels which were irradiated and frozen. These vessels received 300 r. single dose irradiation for the purpose of attenuating their antigenic reaction in the host. This method is based on the observations of Hardin and Werder[8] who found that homografting of irradiated donor skin to normal mice resulted in survival of over one-third of the grafts, in contrast to no survivals over 10 days in the nonirradiated donors.

We undertook this study to test further the possibility that heterograft acceptability might be improved by irradiation.

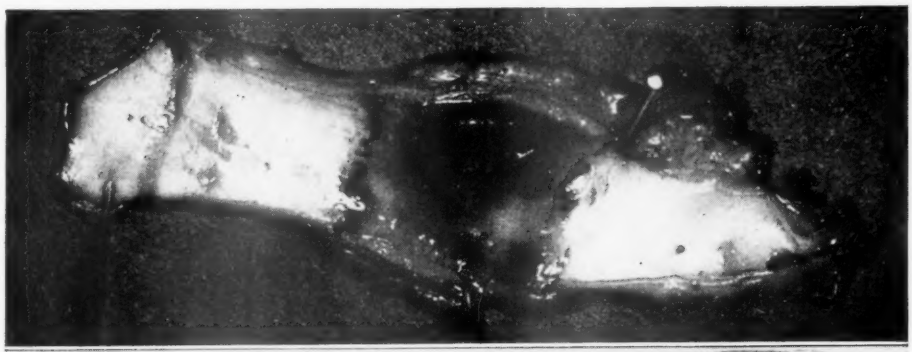
METHOD OF STUDY

Bovine carotid arteries were used because of their easy availability and their close approximation to the caliber of dog aortas. The cow carotids were obtained at the time of slaughter without regard to asepsis. Within 2 hours they were washed, sealed in double polyethylene bags, and frozen at minus 70° F. Sterilization was carried out according to the technique described by Meeker and Gross[12, 13] at the Massachusetts Institute of Technology with the Van de Grafe high voltage cathode ray. A dosage of 2,000,000 r. e. p. was received. The vessels were then stored at minus 70° F. until used. Aortic heterografts were placed in 7 mongrel dogs. Each heterograft was thawed in saline at room temperature at the time of operation and a 3 to 4 cm. segment was anastomosed into the dog aorta from the level of the renal arteries to the trifurcation. Silk sutures (4-0 Deknatel) on Atraumatic needles were used, with a continuous everting mattress stitch that was interrupted at 3 points in the circumference to avoid constriction of the anastomosis. The posterior peritoneum and the areolar tissue were carefully closed over the graft to provide close contact with the host tissues. There was no evidence of spinal cord or hind limb injury due to occlusion of the aorta. No anticoagulants or antibiotics

were used. Five dogs were sacrificed in about 30 days. Two died suddenly of hemorrhage from the anastomotic suture line; one death was definitely due to sepsis.

At necropsy, all of the grafts were encased in a mass of firm inflammatory tissue. In one, several loops of small bowel were adherent. There was no frank exudate or pus except in Dog No. 6, where the graft was covered with bloody

Fig. 1.



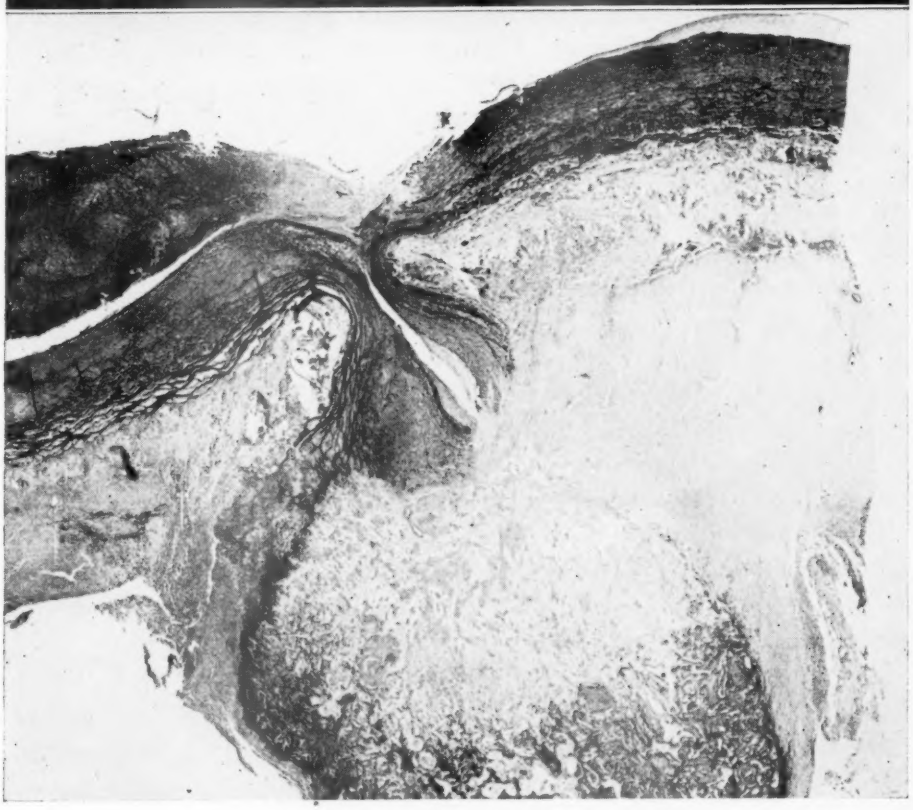


Fig. 2.

Fig. 1.—Typical gross appearance of thrombus-lined heterologous graft.

Fig. 2.—Elastic tissue stain of microscopic section through anastomosis. Graft at left is seen lined with thrombus. There is homogenization of graft media with total acellularity and with fragmentation of elastic fibers. There are no recognizable muscle cells. The intima has completely degenerated and the lining layer (excluding the thrombus) is the internal elastic lamina. The adventitial elastic tissue is abnormally compact due to loss of interposed cells. Inflammatory infiltration of the adventitia of the graft extends into the media.

purulent material. The grafts were removed with a segment of host aorta on each end and sectioned longitudinally. Organized mural thrombus of varying thickness covered the entire inner surface of the graft and ended abruptly at the junction with the host vessel. But the lumen was present, though small, in all of the grafts and the distal arterial tree was patent. Grossly, there was no evidence of dilatation or stricturing of the graft, though it seemed a little early for this to occur. Microscopic sections revealed a low-grade chronic inflammatory reaction in the adventitia that did not extend into the media. The cellular exudate consisted mostly of lymphocytes and round cells with an occasional polymorphonuclear cell. No foreign body giant cells were seen. The media was an acellular hyalin mass, containing condensed and fragmented elastic fibers. There was no evidence of an intima remaining, and an organizing thrombus was densely adherent to the elastica interna. Though the walls were amorphous and acellular, there was no evidence of tearing or rupturing of the grafts.

DISCUSSION

The results of these experiments further confirm the findings contained in other reports on the use of heterografts. For the most part, transplanted blood vessels from one species to another fail to maintain their intended function. Although initial success may be noted for a protracted period of time, the general state is that of degeneration and/or thrombosis. The host reaction to heterografts seems to be one of violent rejection rather than tolerant acceptance, as is seen in homografts. The method of preservation seems to bear little relationship either to the successful survival of the graft or to altering the antigenic reactions of the vessels, except possibly in the methods of alcohol preservation and ethylene oxide freeze-dried preservation.

Despite the heavy irradiation of these grafts, the mechanism involved appeared to be an intense inflammatory host reaction to foreign protein with mononuclear cellular infiltration of the adventitia and with hyalin degeneration of the vessel wall. It is feasible that a lesser, or perhaps greater, exposure to irradiation may favorably alter the antigenic reaction of the heterografts, but this seems unlikely. However, if the foreign protein fraction could be rendered nonantigenic (either by its alteration or by its complete elimination after deproteinization) it seems plausible that the host tissue might infiltrate the walls of the heterograft, restore its lining, and thus maintain its integrity and patency.

SUMMARY

Bovine carotid arteries were prepared by the freeze irradiation method and transplanted into aortas of 7 dogs. They were all found to be thrombogenic. Grossly, the heterografts were enveloped in a mass of intense inflammatory tissue of nonbacterial nature, suggesting an antigenic inflammation to foreign protein. Microscopically, there was complete hyalin degeneration of the vessel and fragmentation of the elastica. The outer surface was surrounded by a low-grade inflammatory reaction, and the inner surface was lined with an organizing thrombus. There was no evidence of infiltration fibroblasts.

It is thought that the failure of the heterografts is primarily due to the species differences in tissue protein which cause the host to produce an intense antigenic inflammation. The frozen irradiation method of preservation and sterilization does not alter this relationship, and eventual fate is that of degeneration and thrombosis.

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TEFLON FABRIC GRAFTS IN GROWING PIGS

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PLIABLE plastic fabrics are gaining increasing recognition as arterial prostheses. They seem to have marked advantages over arterial homografts for specific areas. The fabric is simple to procure, store, and transport and is adaptable to most clinical situations by fabrications in the operating room. Also, the fate of the fabric seems to be more predictable and satisfactory.

Many fabrics of thermoplastic materials are available and have been used experimentally, including nylon, Orlon, Dacron and Teflon. Teflon has been shown to have remarkable chemical inertness and impermeability. Animal experimentation has demonstrated that it causes minimal tissue response after implantation.[5] Previous work in adult dogs using Teflon to replace portions of the thoracic aorta has shown it to be superior in most respects to any grafting material previously tested.[2] In 4 to 6 months the Teflon grafts are covered by a thin fibrous layer on the outside while a translucent, smooth, stable membrane lines the interior. This inner membrane is not unlike the endothelial layer of the adjacent aorta. Complications were minimal and there were no delayed thromboses, ruptures, calcific stenosis, distortion, nor angulation.

The present project was undertaken to determine the fate of Teflon as an arterial prosthesis in growing animals. In order to prevent a relative stenosis by the fabric as the aorta grew, a longitudinal strip autograft was compiled with the fabric. Previous reports have shown the autograft growth will maintain a graft diameter somewhat commensurate with the adjacent host vessel.[3]

METHODS AND MATERIAL

The Teflon fabric used in this experiment is a smooth, tightly woven taffeta. Manufacturer's labels of T-8 and T-10 were used.† T-8 has a thread count of 76 by 65, a thickness of 0.0091 inch, and a porosity of 1.86 cubic feet of air per minute. T-10 has a thread count of 142 by 44, a thickness of 0.0167 inch, and a porosity of 1.86 cubic feet of air per minute. A portion of the fabric was scrubbed in Septisol and water to remove all additives from the fibers, then sterilized by autoclaving for 20 minutes.

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†Manufactured by E. I. duPont de Nemours and Company, Arlington, N. J.

OPERATIVE TECHNIQUE

Nine weaned pigs weighing between 15 and 18 Kg. were used. They were anesthetized by open drop ether and maintained on an oxygen-ether mixture given by a mechanical oxygenator through an endotracheal tube. Through a left fifth intercostal thoracotomy, the descending aorta was mobilized and the intercostal arteries were severed between ligatures. Portions of the mobilized segment were excised between coarctation clamps.

The graft was prepared by cutting a piece of the sterilized Teflon fabric so that the cuffed ends would be the same length as the excised portion of aorta. A longitudinal strip of the excised aorta was cut then. This ranged in width from 1.0 to 2.4 cm. This autogenous strip sutured longitudinally to the cuffed edges of the Teflon so that the combined circumference of the autograft and fabric was equal to the circumference of the host vessel (Fig. 1). This

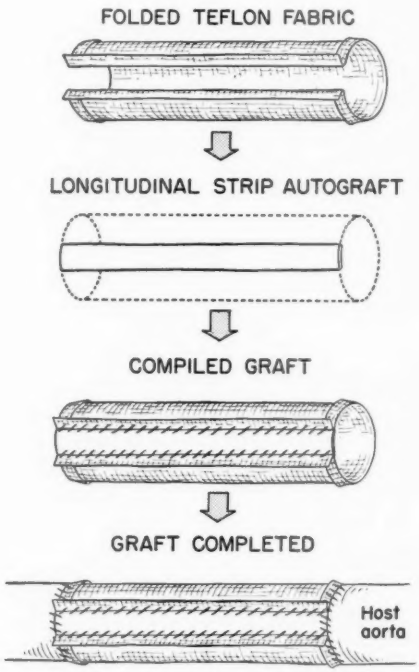

Fig. 1.—The Teflon fabric is sutured to the strip of the excised portion of the aorta. The compiled graft is then sutured to the severed ends of the host aorta.

compiled tube was sutured to the host aorta using an intraluminal polished Lucite shunt for the distal anastomosis and two-thirds of the proximal anastomosis. The shunt was removed then and the proximal anastomosis was completed while the aorta was again occluded by coarctation clamps. All suturing was done with 5-0 arterial silk on an atraumatic needle using a continuous whipstitch.

A single black silk suture was placed exactly 1 cm. from each anastomosis on the aorta to enable measurement of longitudinal host vessel growth. The aorta was covered by pleura. The chest was closed carefully. The lungs were re-expanded and intrathoracic air was removed by a temporary chest catheter.

TABLE I

PIG NUMBER	OPERATIVE				AUTOPSY				GROWTH PER CENT				CHARACTERISTICS				
	FABRIC	GRAFT DIAMETER (CM.)	GRAFT LENGTH (CM.)	AUTOGRAFT, PER CENT OF CIRCUMFERENCE	SURVIVAL DAYS	GRAFT DIAMETER AT AUTOPSY (CM.)	HOST DIAMETER AT AUTOPSY (CM.)	AUTOGRAFT LENGTH	AUTOGRAFT WIDTH	AUTOGRAFT, PER CENT OF CIRCUMFERENCE	HOST LENGTH	HOST DIAMETER	BOWING	CALCIFICATION	ENDOTHELIUM	COMMENTS
367	T–10	1.1	3.1	28	230	2.3	1.8	31	400	68	80	80	+	0	+	Sacrificed
368	T–10	1.4	5.0	24	30	1.4	1.4	0	0	24	0	0	0	0	+	Died*
369	T–10	1.1	4.4	31	226	1.8	2.0	18	260	62	80	80	+	0	+	Sacrificed
370	T–10	2.0	3.1	29	223	1.8	1.7	3	180	53	50	50	0	0	+	Sacrificed
371	T–10	1.5	3.3	50	220	4.4	2.2	24	200	76	100	75	+	0	+	Sacrificed†
372	T– 8	1.2	6.2	42	20	1.2	1.2	0	0	42	0	0	0	0	+	Died, unknown cause
373	T– 8	1.3	3.0	35	45	1.6	1.6	6	53	47	20	23	0	0	+	Died, empyema
377	T– 8	1.4	3.3	40	294	2.1	2.0	28	130	61	60	50	+	0	+	Sacrificed
378	T– 8	1.5	7.0	31	293	2.7	2.4	3	250	61	30	66	+	0	+	Sacrificed
Average			4.2	34.4				16.1	213	61.3	58.5	60.5				

*Animal died on the thirtieth postoperative day of a thrombosis at distal shunt tie mark.
†Animal was slaughtered and a small, 7 mm. deep aneurysm was found in mid-portion of autograft strip.

Each pig was given a single injection of a long-acting penicillin preparation postoperatively. Ambulation and food were permitted as soon as the animal recovered from the anesthetic.

OTHER STUDIES

Ambulation was carefully observed postoperatively in order to detect any neurologic signs indicating spinal cord damage from excessive aortic occlusion during operation or thrombus formation subsequently. Femoral pulses were palpated weekly for 4 weeks; then the animals were sent to a farm. They were sacrificed at slaughter 7 to 10 months postoperatively when they were suitable for marketing. The descending aortas were salvaged and studied.

RESULTS

The results are presented in Table I. Blood loss was minimal through the fabric and anastomoses, averaging about 100 c.c. No difficulty was encountered with uncontrollable blood loss through the compilation suture line and rarely was additional suturing required.

Endothelization of the fabric occurred not only from the ends of the host vessel but apparently from the longitudinal autograft as well. At the end of 4 weeks, the inner surface of the graft was totally covered by a smooth, translucent, shiny layer (Fig. 2). This rapid growth of endothelium may be due in part to the youth of the host or a species peculiarity since 6 months were required for complete endothelization in adult dogs.

The autograft strip grew well. The strip comprised an average of 34 per cent of the circumference initially but was 61 per cent of the graft's circumference when sacrificed. While the average growth of the adjacent host vessel was about 60 per cent, the transplanted strip grew an average of 16 per cent in length and an average of 213 per cent in width. The longitudinal growth created some minor bowing of the graft with the fabric being on the concave side, but no serious deformity ensued (Fig. 3). The remarkable growth or stretching of the width of the transplanted aortic strip made all of the grafts nearly isodimensional with the adjacent host vessel.

The fibroblastic response was greater in these growing pigs than that previously observed in adult dogs. In dogs, the reaction layer was so thin that many of the grafts were visible beneath the pleura when sacrificed; but in these pigs, most of the grafts were covered by a 2 mm. thickness of a whitish, fibrotic covering. This covering, however, was seen throughout the periaortic dissection area and may be reflective of the usual healing process rather than any unusual foreign body response. No calcification was found in any graft.

Wrinkling in the fabric grafts in growing pigs was reported by other investigators.[3] However, care was taken that the graft was as long as the resected portion, and no wrinkling was found in this series.

There was no difference observed between the 2 weaves used. These fabrics are of considerably lower porosity than many of the Orlon, Dacron, and nylon fabrics tested.[1, 4, 8] No problem was encountered in making the multiple, perpendicular creases, nor in making any of the anastomoses. While

the endothelium and external fibrous layer grew readily into the fabric interstices in a matter of a few weeks, these layers were always separable from the fabric. This quality was not found to be a problem, and does not seem to be a contraindication for using low porosity fabrics.

Fig. 2.

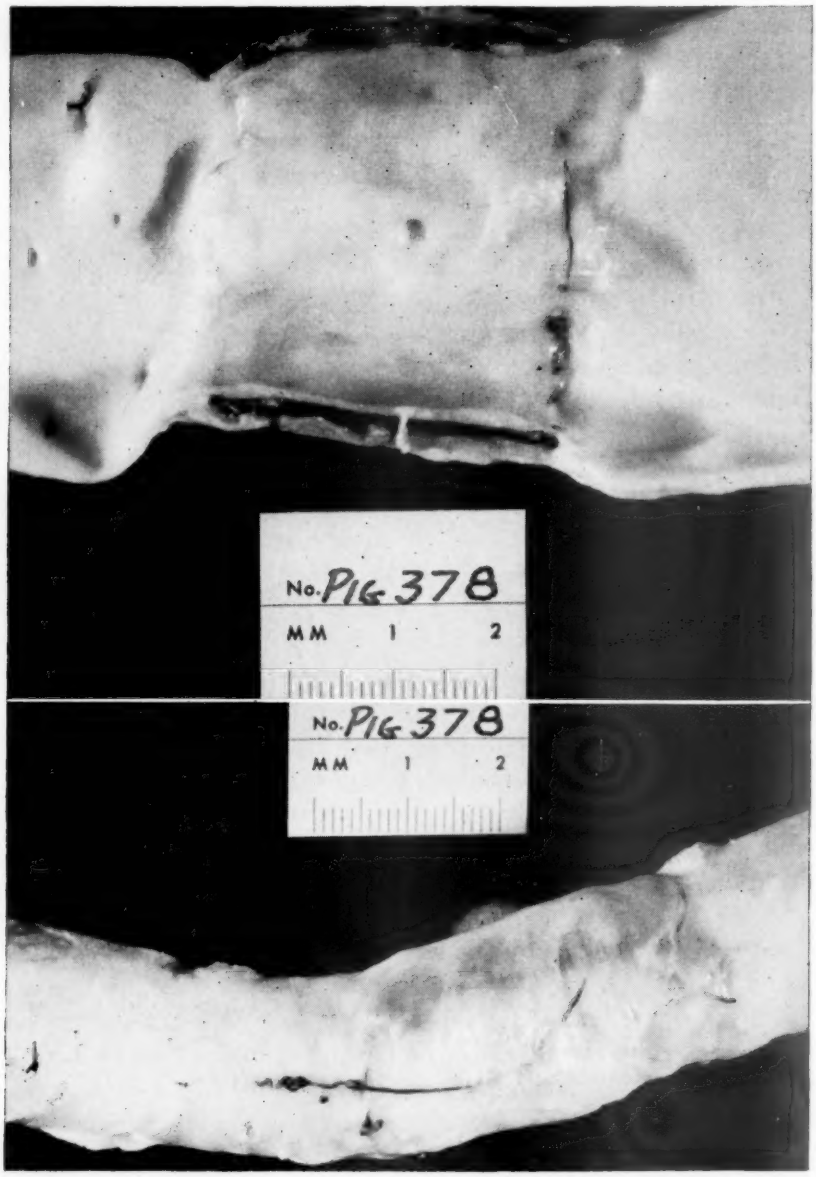

Fig. 3.

Fig. 2.—This specimen is from a pig 293 days postoperatively and clearly shows the smooth inner lining of the fabric which is indistinguishable from the centrally located autograft. Note the relatively thin fibrous outer covering.

Fig. 3.—This inflated graft, 293 days old, shows the slight curvature caused by the longitudinal growth of the autograft but also shows the isodimensional measurements of the graft and host vessel.

Only one thrombosis causing death occurred in the group. This thrombosis occurred at the site where the intima was crushed by the distal shunt tie and did not involve the graft. Two other animals died before maturity. One died 20 days postoperatively of an unknown cause and the other succumbed 45 days postoperatively of empyema. This infection was on the same side as the surgery, but the graft did not seem to be the nidus.

DISCUSSION

Teflon seems superior in most respects both during placement and over long-term studies to other arterial grafting materials. Each of these separate experimental studies have demonstrated the unusually small amount of foreign body reaction around the fabric not only in adult dogs but in growing pigs. Within a few months the fabric is incorporated in the surrounding tissue by only a slight amount of fibrous tissue and does not stimulate calcification nor delayed thrombosis. It provides a stable, satisfactory graft in nearly every case.

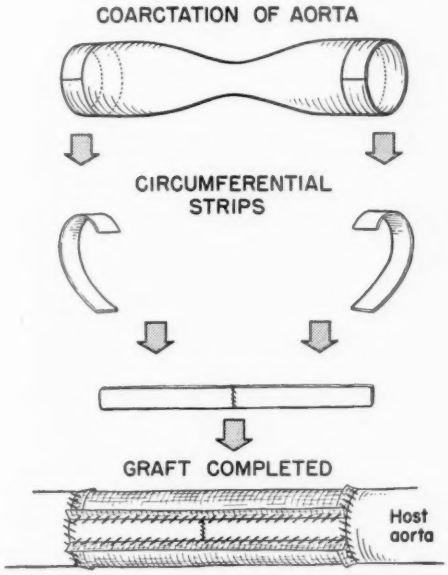

Fig. 4.—A schematic drawing of the theoretic application of a compilation graft incorporating a longitudinal autograft and Teflon fabric. After the coarctation is removed, suitable strips are cut from the aorta, opened, and sutured together to form a compilation graft with Teflon.

Grafting is occasionally necessary in growing patients during the resection of coarctation of the aorta. Homografts have been used for this purpose. They are not viable and do not grow; also they present many degenerative complications. Many of these such as subintimal calcification, cracking and thrombosis can reduce or destroy the value of the grafts. Tubes of Teflon undoubtedly would be satisfactory grafts in these young patients, but the addition of the strip autograft may be an even more satisfactory graft in this situation (Fig. 4). Previous work indicates that the autograft compilation is as satisfactory when the strip is composed of longitudinal strips from the vessel or made of circumferential segments turned longitudinally.[7] The excessive

growth observed in the width of the autograft is probably a response to the intraluminal pressure. However, it is well adjusted since only one slight aneurysm was found and the remaining grafts were remarkably isodimensional. There was no immediate danger of rupture or mural thrombus in the one small aneurysm found.

Teflon is not only more convenient and economical than homografts, but is also more adaptable to a variety of clinical situations. Furthermore, the long range results are highly satisfactory. The longest graft observed in this series was 293 days, but there are grafts up to 12 cm. long performing satisfactorily in dogs over 24 months after implantation. The first replacement in the human has been implanted over 15 months without complication.[6]

CONCLUSIONS

1. Teflon fiber is a most chemically inert, nonpermeable material. As a low porosity taffeta weave, it serves as a highly satisfactory aortic prosthesis.

2. No untoward reaction was found to Teflon in the growing pig.

3. Compilation grafts consisting of two-thirds fabric and a one-third longitudinal strip autograft provided a growing isodimensional graft in this series of pigs.

4. A thin endothelial-like membrane covered the interior of the fabric and dense noncalcific fibrous layer coated the exterior. No wrinkling or serious distortion of the fabric graft occurred in any animal.

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THE EXPERIMENTAL USE OF IVALON ARTERIAL GRAFTS

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THIS report concerns experiences with 130 Ivalon* arterial grafts which were inserted into the thoracic and abdominal aortas of dogs. Of the many substances that have been used for arterial grafts, a polyvinyl plastic, Ivalon, has been very promising. The early work with Ivalon in experimental animals and plastic, cardiac, and thoracic surgery reveals it to be extremely well integrated when implanted into living tissue.[2, 3, 10-14, 16-18, 20] Numerous authors have reported encouraging results with the use of Ivalon tubes for arterial grafts, both in experimental animals and in clinical cases.[4, 5, 8, 15, 17-19, 21-24, 26-30] The results of this report differ in some aspects from previous ones.

The method described by Shumway[30] was utilized in making the Ivalon tubes suitable for arterial grafts in this series. The Ivalon block is repeatedly rinsed, frozen, and sliced with an ordinary meat slicer into thin sheets approximately 2 mm. thick. A sheet of Ivalon is then wrapped around a metal tube of suitable diameter; approximately 4 layers are required. An external splint with a diameter larger than the tube is then placed around the Ivalon compressing it. The apparatus is placed in distilled water and sterilized at 250° F. for 20 minutes. During this time not only does sterilization take place, but fusion of the Ivalon is achieved which causes it to retain its tubular shape. The main difficulty concerned the decision about the thickness of the wall of the Ivalon tube and exactly how much Ivalon should be compressed. Some compression is obviously necessary because commercial Ivalon does not possess sufficient strength to withstand arterial pressure.[6, 7] On the other hand, if Ivalon is compressed too much, this elastic permeable material will be converted into a rigid impermeable tube. Although not definitely ascertained, it appears reasonable that suitable arterial substitutes should be elastic and must have at least some tissue permeability for the ingrowth of fibrous tissue.[1, 9, 32] Ivalon demonstrates both of these properties unless it is compressed too much. At first the Ivalon was compressed to the same thickness as the host artery, approximately 1.5 mm. Unfortunately, this amount of compression converted the tubes into a rather rigid impermeable structure. By trial and error, it was found that if the wall thickness of the Ivalon graft was made approximately 3 times that of the host artery (3 to 5 mm.), better results were obtained. This increased thickness would give sufficient strength of a loosely compressed Ivalon retaining the desirable properties of elasticity and permeability. Because the density of the Ivalon graft was considered so important, the following method was devised to standardize the density. The weight of

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*Clay Adams Company, New York, N. Y.

the Ivalon graft was obtained while saturated with water and after air drying. The weight of the dry graft was divided into the weight of the water attracted by the hydroscopic properties of Ivalon. The resulting figure is called the density coefficient. After many attempts, it was found that a density coefficient of 2 $\pm$ 0.5 was most suitable. A graft with this density would mildly weep blood through its substance for 30 to 60 seconds. The graft would also pulsate with systolic blood pressure and retain a high degree of tissue permeability.

Ivalon grafts with a wall thickness approximately 3 times greater than the host artery created a problem in making the anastomosis. A modified continuous everting suture was devised (Fig. 1). The Ivalon tubing will not lend itself to the same eversion observed in the host artery. The host artery was everted against the flush end of the Ivalon graft and sutured in this position with continuous everting mattress sutures so that the needle was inserted on the flush end of the graft near the lumen. In this fashion, the suture material was not visible from the lumen and there was no lumen discrepancy between the host artery and the graft. It is realized that this type of suture may not always be feasible in clinical cases where the vessels are diseased, but a simple over-and-over suture should then prove to be satisfactory.

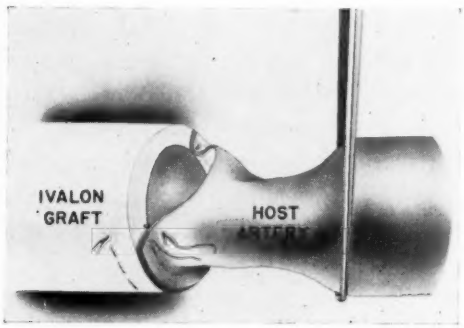

Fig. 1.—Modified continuous everting mattress suture used with Ivalon grafts.

The Ivalon grafts were placed in the abdominal aorta between the renal arteries and trifurcation and in the thoracic aorta. Grafts 3 cm. in length were used and the circulation was interrupted for 20 minutes. Paraplegia did not follow the insertion of the abdominal grafts unless thrombosis appeared. Approximately 20 per cent of the animals were rendered paraplegic during the insertion of the thoracic graft. Whenever thrombosis occurred and death did not ensure immediately, the animal was sacrificed aseptically and cultures of the graft site were taken to determine if infection could be the cause for failure. Microscopic study was performed in all grafts to confirm the thrombosis and to determine the cause of the thrombosis, if possible. Surviving animals were checked at 3 months for patency of the graft by arteriograms (Figs. 2 and 3). If any doubt occurred concerning patency, the animal was sacrificed. The abdominal aortic grafts were first visualized by using posterior percutaneous puncture of the aorta (Fig. 2). This procedure was followed by a high incidence of paraplegia as reported by Tarazi[31] and was discontinued. The best method to visualize both the abdominal and the thoracic grafts proved to be the percutaneous injection of 10 c.c. of 70 per cent Urokon directly into

the left ventricle (Fig. 3). Films exposed immediately after the injection revealed good visualization of the entire aorta. For a control group, freeze-dried ethylene oxide-treated homografts were selected and otherwise executed in similar fashion.

Fig. 2.

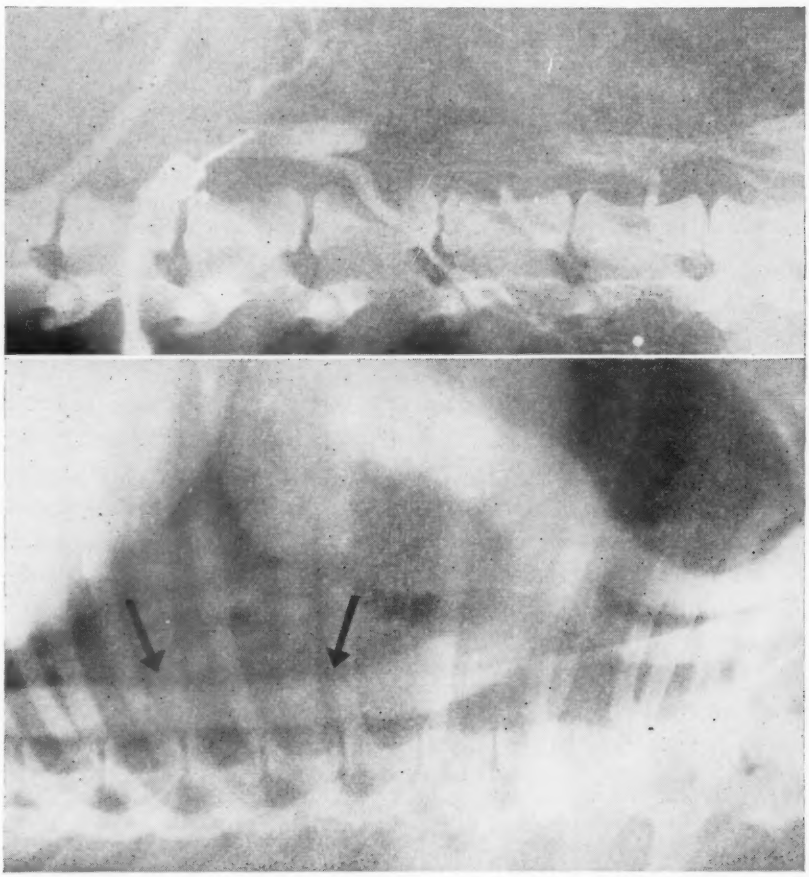

Fig. 3.

Fig. 2.—Aortogram reveals occlusion of Ivalon graft in the abdominal aorta of dog.
Fig. 3.—Cardioangiogram 3 months after successful insertion of Ivalon graft in the thoracic aorta of dog.

RESULTS

Although 130 Ivalon grafts have been implanted in the arteries of dogs, many failures occurred during the learning process. Infection remained a problem and was usually followed by hemorrhage from the suture line during the postoperative period. In 3 cases the Ivalon graft ruptured and in 2 cases aneurysms developed but the density coefficient revealed the graft to be too thin and these cases were considered technical failures. If any technical error was detected it was excluded from the series. Of the 130 grafts, 60 appeared to have been properly executed. Three months after implantation primary thrombosis had occurred in 23 of the 60 grafts. No technical error except the Ivalon graft itself could be found to explain these thromboses. A study of the thrombosed grafts revealed that the majority of the thromboses occurred

when the graft was inserted in the smaller arteries. If the grafts are divided into 2 groups, those having internal diameter of 4 to 8 mm. and those 8 to 12 mm., it was found that 22 of the 23 failures occurred in smaller arteries (Table I). Sixteen homografts with an internal diameter of 4 to 8 mm. functioned 3 months with one failure.

TABLE I. RESULTS OF ARTERIAL GRAFTS THREE MONTHS AFTER INSERTION

TYPE OF GRAFT	INTERNAL DIAMETER OF GRAFT	NO. GRAFTS	SUCCESSFUL	FAILURES	SUCCESSFUL (PER CENT)
Ivalon	4 to 8 mm.	42	20	22	48
Ivalon	8 to 12 mm.	18	17	1	94
Freeze-dried homograft	4 to 8 mm.	16	15	1	94

DISCUSSION

The high failure rate (38 per cent) of Ivalon arterial grafts in this series is at variance with Shumway's report[30] in which only one failure occurred in 14 grafts at 3 months and Mortensen's report[21, 22] in which there were no failures in 17 grafts at 9 months. This discrepancy could be explained by the size of the arteries since failure rate in large arteries is only 6 per cent in this series. Neither author recorded the dimensions of grafted arteries but both included "Y" grafts of the aortic trifurcation which is always a small artery in the dog. Freeze-dried arterial homografts were selected for a control group because 97 per cent successes were reported by Pate[25] in a large series of dogs. This control series in small arteries was 94 per cent successful. This study, agreeing with Pinkham,[26] suggests that Ivalon is satisfactory for grafting arteries the size of the common iliac or aorta in man, but it should not be used in smaller arteries. Freeze-dried arterial homografts are superior especially in small arteries.

SUMMARY

1. Ivalon arterial grafts have been successfully placed in 60 animals.

2. The study of the results obtained suggests the following:

a. Ivalon arterial grafts are 94 per cent successful when the internal diameter of the vessels is more than 8 mm.

b. Ivalon arterial grafts are only 48 per cent successful when the internal diameter is smaller than 8 mm.

c. Ivalon grafts should probably not be used in man unless the artery is the size of the human common iliac artery or larger.

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A RESPIRATOR FOR LABORATORY ANIMALS UTILIZING COMPRESSED AIR AND SUCTION

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THE serious sequela of respiratory acidosis noted in human patients during open thoracotomy and general surgical operations[1] has also been encountered during surgical procedures in experimental animals. The accumulation of carbon dioxide in alveolar gas as a result of inadequate ventilation of the lungs during anesthesia appears to be the most important single factor.[2] The ventilation produced by the rhythmic insufflation of the lungs with room air and unassisted expirations during open thoracotomy in laboratory animals has been found to be frequently incapable of consistently preventing or correcting respiratory acidosis, and in many cases, fails to provide adequate saturation of arterial blood with oxygen. Under such conditions, voluntary respiratory efforts continue because of continued stimulation of the carotid bodies and respiration center. The inability to synchronize the breathing of the subject with the function of the respirator results in a further decrease in tidal exchange and worsening in general condition.

The respirator to be described utilizes compressed room air and suction as a means of rapidly and more completely removing the expired gases from the lungs and tracheobronchial tree. The improvement in ventilation is evidenced by apnea, a reduction in the partial pressure of carbon dioxide, and an increase in partial pressure of oxygen in arterial blood. The respiratory movements are then produced solely by the respirator. In nearly all instances the arterial blood is either saturated or supersaturated with oxygen. This device has consistently maintained a low partial pressure of carbon dioxide and high saturation of arterial blood with oxygen in a large number of intrapleural operations in dogs. All dogs have been apneic during and for a short period after discontinuance of insufflation.

APPARATUS

The respirator (Fig. 1) is supplied with compressed air at 5 lbs. line pressure. Since apnea is consistently produced, the frequency of insufflation of the lungs must be controlled by a timing device. The timing circuit, consisting of a conventional electronic multivibrator, alternately opens and closes electrically operated solenoid valves (*C,G*) interposed in the inspiratory and expiratory pathways of the gas circuit. The frequency of the multivibrator may be varied between 5 and 25 respiratory cycles per minute by a control provided for that purpose. An additional control varies the dwell time of each half of the cycle

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in such a fashion that a change in the duration of one phase is automatically compensated by altering the period of the other phase without changing the frequency. The expiratory phase is usually 20 per cent longer than the inspiratory phase.

During inspiration the solenoid valve (*G*) opens, introducing room air into the animal's lungs, and the solenoid valve (*C*) closes. The gas flow through the circuit can be regulated by manually controlled pressure valves (*A* and *H*). The maximum intrapulmonary air pressure during inspiration is controlled by the spring loaded valve (*D*).

During expiration the solenoid valve (*G*) closes and the solenoid valve (*C*) opens. The full line pressure is then diverted to the venturi jet (*B*) which produces suction and rapidly exhausts expiratory gases from the lungs. The rate with which the expired gas is withdrawn can be regulated by the pressure control valve (*A*). The final degree of vacuum attained within the trachea and lungs at the end of expiration is again limited by the spring loaded valve (*D*). The water manometer (*E*) indicates the pressure gradients during the respiratory cycle. The height of the water column is greater than the maximum intrapulmonary pressure attained.

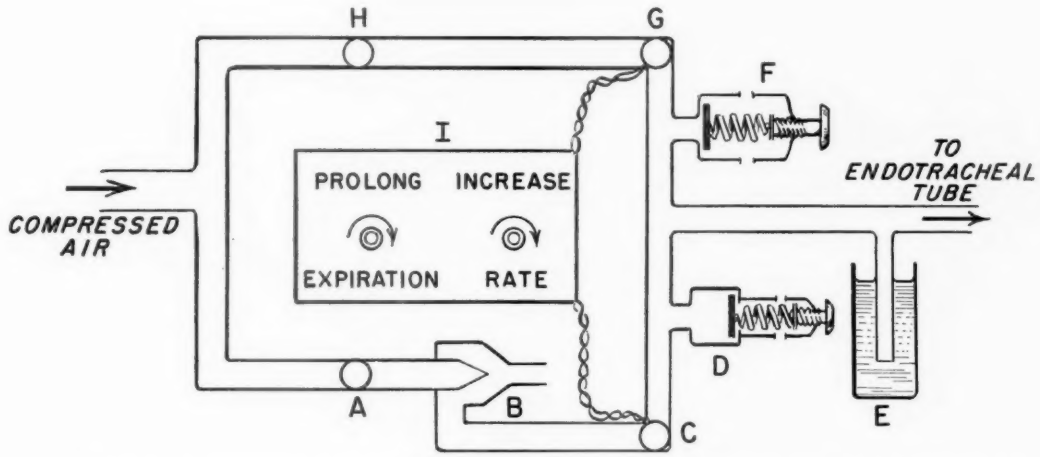

Fig. 1.—An improved laboratory respirator. *A*, Manual control valve, *B*, venturi jet, *C*, solenoid valve, *D*, negative pressure relief valve, *E*, manometer, *F*, positive pressure relief valve, *G*, solenoid valve and *H*, manual control valve.

PROCEDURE

Anesthesia was induced with an initial intravenous injection of 25 mg. of sodium pentobarbital per kilogram of body weight. Small supplemental doses were administered intravenously to abolish the lid reflex. An endotracheal tube with inflatable cuff was placed within the trachea.

The animals were placed in the supine position and cannulae were placed within the femoral artery and vein in a cephalad direction. The initial arterial and venous blood samples were used for the determination of oxygen content, oxygen capacity, carbon dioxide content, and pH while the dog was breathing spontaneously through the endotracheal tube. The endotracheal tube was next

connected to the respirator and blood samples were withdrawn at intervals while the respiratory function of the subject was maintained by the respirator.

The pH of the blood was determined immediately after withdrawal from the femoral artery and vein by means of a pH meter. The reduplicable accuracy of this instrument is .02 pH unit. Oxygen content, oxygen capacity, and CO_2 content were determined by the method of Van Slyke and Neill.[3] The P CO_2 was obtained from the nomogram of Van Slyke and Sendroy.[4] In instances where the P CO_2 could not be obtained from the nomogram because of unusually high pH values, it was necessary to calculate P CO_2 from the Henderson-Hassellach equation. The rate of insufflation was maintained at 20 per minute, the pressure at the end of inspiration was maintained at 12.6 cm. of water, and the pressure at the end of expiration was–2.5 cm. of water.

In experiments in which the thorax was widely opened, the animals were placed in the left lateral position after cannulation of the femoral vessels. A thoracotomy was performed with removal of the right fourth rib. The pleura was opened and a rib spreader inserted which provided a wide communication of the pleural cavity with the atmosphere. In these experiments the same studies of arterial and venous blood were made before connecting the animal to the respirator, prior to opening of the pleura, and during the time the pleural cavity was in communication with the atmosphere.

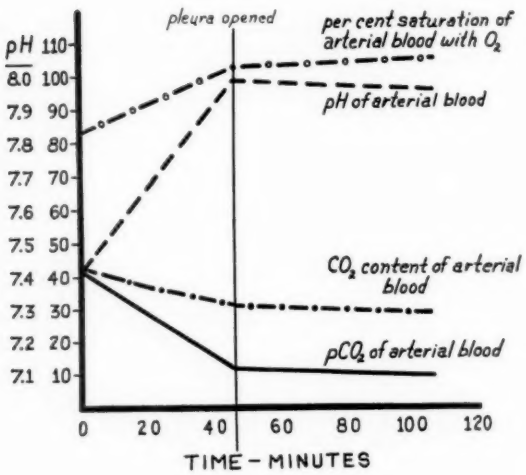

Fig. 2.—Open chest.

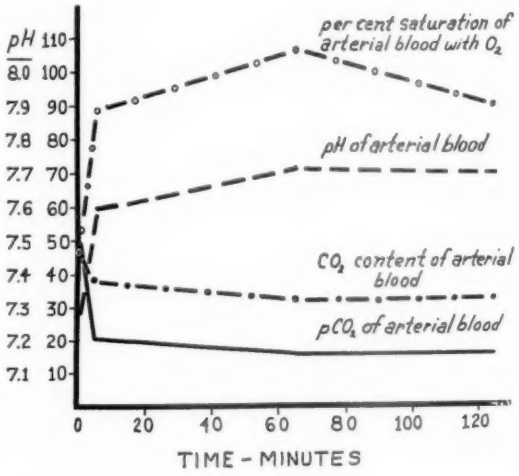

Fig. 3.—Closed chest.

RESULTS

The graphs shown in Figs. 2 and 3 are representative of the ease with which adequate ventilation can be maintained in experimental animals anesthetized with sodium Pentothal during closed and open thoracotomy. At an insufflation rate of 20 per minute, an abnormally low partial pressure of carbon dioxide is consistently attained in arterial blood. Spontaneous respirations ceased during the first 2 or 3 cycles of the respirator in all instances. The saturation of arterial blood with oxygen has been consistently above 92 volumes per cent when room air was used for insufflation of the lungs. The improved

ventilative efficiency of this respirator is evidenced by the rapid rise in pH of arterial blood accompanied by a concomitant fall in the P CO_2 in arterial blood.

Of equal significance is the ease with which intrathoracic surgical procedures can be accomplished. Movements of the mediastinum noted when the ventilatory efficiency of conventional respirators was insufficient to eliminate the subject's own respiratory efforts are completely eliminated during respiration with this device. Both lungs are equally insufflated and the mediastinum remains motionless.

SUMMARY

1. This respirator described utilizes suction as a means of ventilating laboratory animals anesthetized with sodium Pentothal.

2. The saturation of arterial blood with oxygen during artificial respiration with room air is consistently above 92 volumes per cent when the respiratory rate is 20 per minute.

3. The subject becomes apneic within the first 30 seconds of artificial respiration.

4. A sharp rise in the pH of arterial blood occurs within 5 minutes of artificial respiration. This is associated with a fall in the P CO_2 of arterial blood.

5. Arterial blood is adequately saturated with oxygen during artificial respiration.

6. The subject remains apneic for at least 90 seconds after the termination of artificial respiration.

7. The possible use of this device for ventilation during thoracic surgical procedures in patients and for the resuscitation of infants is suggested.

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STUDY OF THE CANINE LUNG AS AN OXYGENATOR OF HUMAN AND CANINE BLOOD IN EXTRACORPOREAL CIRCULATION

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THE use of a heterologous lung as a biologic oxygenator for extracorporeal circulation, suggested by Mustard[5] and Potts,[8] has been evaluated by several works.[1, 6, 10, 11] Our preliminary experiments showed that oxygenation of human blood with a dog lung was possible and suggested a thorough evaluation of the homologous lung as an oxygenator for the dog. We found that with proper care the dog lung is an excellent oxygenator for cardiopulmonary by-pass in the dog. We have not, however, been able to perfuse the dog lung satisfactorily with sufficient quantities of human blood to make its clinical use practical.

METHOD

Perfusion of Dog Lung With Dog Blood.—Sixty-nine experiments were done in which the heart and lungs of a recipient dog were by-passed through a Dale-Shuster type pump with a donor dog being used as an oxygenator.

Healthy mongrel dogs weighing between 6 and 10 Kg. were used as lung donors. Ether and air anesthesia was given with a mechanical positive pressure respirator. With sterile operative technique the chest was opened through the left fifth intercostal space, the pericardium was opened, and the aorta and the pulmonary artery were isolated. After 3 mg. of heparin* per kilogram of body weight were given intravenously, the pulmonary artery was cannulated through a stab wound in the outflow tract of the right ventricle. The stainless steel cannula (3/8 inch inside diameter, 0.020 inch wall thickness) was held in place by a purse-string suture in the ventricle. Since it did not completely obstruct the pulmonary artery, the circulation continued until all cannulations were completed and the donor lung was ready for use.

A similar cannula was placed in the left atrium through the appendage and held in place by a purse-string suture. Small polyethylene cannulae were placed in branches of the pulmonary artery and vein through which pressures were measured on Statham strain gauges and recorded on a Sanborn Polyviso recorder. Monitoring the pulmonary venous pressure aided in correction of the position or angulation of the cannulae should obstruction and increased pressure appear. Following exsanguination of the donor animal the ascending aorta was ligated and the pulmonary artery tied over the stainless steel cannula.

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*Kindly furnished by The Upjohn Company, Kalamazoo, Mich.

Concurrently with preparation of the donor animal the femoral artery and vein of a dog serving as recipient ranging between 10 and 18 Kg. were cannulated for measurement of pressure, and the chest was opened through the right fourth intercostal space. The right subclavian artery, azygos vein, and superior and inferior venae cavae were isolated, and the pericardium was opened. After 3 mg. of heparin per kilogram of body weight were given to the recipient, a 3/16 inch, 0.020 wall thickness curved stainless steel cannula was introduced into the proximal subclavian artery. Polyvinyl catheters, 3/16 inch i.d., were placed through the azygos vein to the superior vena cava and through the auricular appendage to the inferior cava. Tubing in the circuit was polyvinyl chloride,* sterilized by autoclaving at 250° F. for 10 minutes.

After the above preparations and exsanguination of the donor animal, the venous blood of the recipient was led to the pulmonary artery of the donor through ½ inch i.d. tubing. The recipient animal was on a high table, 37 cm. above the level of the donor dog's pulmonary artery. This difference in level produced a pressure in the pulmonary artery of the donor between 20 and 30 cm. of saline at a flow of 850 to 1,500 ml. per minute. From the left atrium of the donor the oxygenated blood flowed by gravity through ½ inch tubing to a small reservoir covered by a thin rubber membrane 15 cm. below the left atrium of the donor. A light iron cylinder attached to the membrane was positioned in an electromagnetic field so that changes in position of the membrane automatically controlled the stroke of the arterial pump. From the reservoir, blood was returned to the recipient subclavian artery by the automatically controlled pump of the Dale-Shuster type. The control was sufficiently accurate to keep the pulmonary venous pressure in the donor lung between 0 and 20 cm. of saline with an average of 10 cm. of saline. A Monel metal filter (100 mesh screen) was connected in the tubing between the arterial pump and the subclavian artery.

Air was prevented from entering the circuit, particularly during cannulation. On the venous side air emboli caused a capillary block of the lung; on the arterial side they were returned to the recipient's aorta. The circuit was primed with blood taken from the donor animal as well as others killed for this purpose. No cross-matching was done.

After perfusion was started the venae cavae were occluded around the cannulae and a right ventriculotomy was done. Cardiac venous return was aspirated into a reservoir by 15 cm. of water negative pressure and a siphon over a 40 to 50 cm. drop. A pump† returned the blood from the reservoir to the extracorporeal circuit proximal to the donor lung. During perfusion the donor lung was ventilated mechanically with air; ether was administered to the recipient as needed through the donor lung.

Flow in this preparation was determined by the venous return of the recipient animal. This usually amounted to 70 to 118 ml. per minute per kilogram of body weight.

*Tygon S-22-15, U.S. Stoneware Co., Akron, Ohio.
†Model T6S, Sigmamotor Co., Middleport, N. Y.

At the end of 30 minutes the ventriculotomy was sutured and all cannulae were removed from the recipient. The effects of heparin were neutralized by the administration of protamine sulfate; the total dose was 2 mg. protamine per milligram of heparin. Two-thirds of the protamine was given immediately after perfusion in a slow intravenous drip of glucose (50 mg. protamine in 50 ml. of 5 per cent glucose in water). The remainder was given approximately one hour later to counteract the so-called heparin rebound.

Following perfusion the vessels and bronchi of the donor lung were grossly examined. If any sign of edema or of other abnormality was seen, microscopic sections were obtained.

Blood samples during perfusion were analyzed for oxygen content, plasma hemoglobin, pyrogens, and bacteria. Blood volume determinations before and after perfusion were done with T-1824 dye. An additional estimate of blood volume was obtained by weighing the animal before and after perfusion.

Twenty-five of 28 recipient dogs died when the circuit was first used. This mortality was progressively reduced by the following 4 measures:

1. *Elimination of pyrogens:* Injection of perfusate into rabbits showed a strong pyrogen. Nelson[7] had previously described the adverse effects in the cardiovascular system of injections of bacterial products into dogs. These effects were eliminated by using new tubing for each experiment, by thoroughly cleaning all components of the system coming in contact with blood, and by care in preparation of saline used to fill the pump before cannulation.

2. *Treatment of acidosis:* Studies of electrolytes and pH revealed metabolic acidosis (pH as low as 7.00) following perfusion as described by Dennis[9] and by Lillehei.[2] This was corrected by intravenous infusion of sodium bicarbonate 3 to 5 Gm. in 100 ml. of distilled water.

3. *Blood volume determinations:* Loss of weight during the procedure and blood volume estimation with T-1824 dye showed extreme oligemia, often in spite of normal or elevated blood pressure. Transfusions were given to restore the preoperative blood volume plus an additional 2 per cent of body weight (roughly 20 per cent of blood volume). Restoration of blood volume often strikingly improved the acidosis.

4. *Broad spectrum antibiotics:* Broad spectrum antibiotics were given before and after operation. Institution of these 4 measures was associated with a noticeable improvement in the postoperative appearance of the animals. The method seemed adequately tested when 6 consecutive survivals were obtained following a 30-minute right ventriculotomy.

Perfusion of Dog Lung With Human Blood.—The response of the dog lung to human blood was studied in a similar circuit except that a reservoir was used in place of a recipient animal. Twelve mongrel dogs weighing between 8 and 12 Kg. were used as lung donors. Anesthesia and preparation were similar to those used in the preceding experiments except that in 9 dogs the left atrium was cannulated through a left ventricular stab wound through the mitral valve orifice. A purse-string suture around the mitral valve ring was tied over the cannula. This was done in an attempt to eliminate the possibility of

dog blood loculating in the left ventricle and possibly contaminating the human blood through an incompetent mitral valve. This method was more effective in ridding the lung of cells, but in spite of these efforts all microscopic traces of donor blood could not consistently be removed from the circuit.

Pulmonary artery pressure was controlled by the height of the reservoir above it; this was between 30 and 40 cm. Blood thus entered the lung by gravity, flowed through the pulmonary capillary bed, and entered a reservoir 15 cm. below the left atrium. From here it was pumped to the reservoir above the pulmonary artery. The pulmonary venous pressure which was monitored on several occasions showed no evidence of obstruction.

Before perfusion of the lungs with heterologous blood, the pulmonary circuit was cleaned of donor blood by perfusing it with either 5 per cent dextran* in saline or 3.5 per cent polyvinyl pyrrolidine in saline from the reservoir. The amount of plasma expander used was determined by the gross appearance of the perfusate after passing through the lung. After 2 to 4.5 L. were used, only microscopic traces of dog red cells were found.

The lungs were perfused for 30 minutes unless edema became too severe to permit this. Flow initially ranged between 200 and 3,600 ml. per minute although this rate usually fell as edema appeared. In 10 animals whole human blood was used as perfusate. In 8 of these animals the blood contained citrate as anticoagulant. In 2 animals the blood was freshly drawn with heparin as anticoagulant (20 mg. heparin per 500 ml. of whole blood). In one animal plasma was used for perfusion and in another both plasma and blood were used.

Examination of the lungs after perfusion was similar to that in previous method except that microscopic examinations were done routinely.

RESULTS

Perfusion of Dog Lung With Dog Blood.—The results of 12 consecutive experiments in which oxygen saturation, hemolysis, and pyrogen studies were obtained are shown in Table I. In an effort to test vigorously the donor lung, we routinely used a donor dog smaller than the recipient. This usually meant perfusing the donor lung with 100 to 200 ml. per kilogram of body weight of the donor. In spite of this high flow, the lungs of 10 of 12 donor dogs showed no evidence of edema. Two lungs showed gross edema. One of these instances could be attributed to a high pulmonary venous pressure due to inadvertent pulmonary venous obstruction when placing the lungs in the extracorporeal circuit. The other case showed gross edema when air entered the pulmonary artery of the donor lung. Excepting the two lungs which became edematous, oxygen saturation attained by the homologous lung was 78 to 100 per cent. When edema appeared, oxygenation became extremely poor. Perfusion of one set of lungs with 6 per cent dextran in saline before perfusion with blood did not interfere with oxygenation or cause edema.

Hemolysis ranged between 2 and 101 mg. per cent of free hemoglobin with an average of 38 mg. per cent. Pyrogens were tested in 5 animals and found

*Plavolex kindly furnished by Wyeth Laboratories, Inc., Philadelphia, Pa.

TABLE I. PERFUSION OF DOG LUNG WITH DOG BLOOD

NO.	DONOR WEIGHT (KG.)	RECIPIENT WEIGHT (KG.)	FLOW			ARTERIAL O_2		VENOUS O_2		PATHOLOGY		INCREASE IN FREE PLASMA HEMOGLOBIN AFTER PERFUSION (MG. %)	REMARKS
			TOTAL ML./MIN.	ML./KG. RECIPIENT WEIGHT	ML./KG. DONOR WEIGHT	VOL. %	% SAT.	VOL. %	% SAT.	GROSS	MICROSCOPIC		
A-1	8.5	13	1,300	100	153	18.7	95	11.3	55	Normal		33	Survived
A-2	7.5	17	1,400	82	187	14.5	78		78	Normal		23	Survived
A-3	9.0	12	1,400	110	156	20.0	81	14.0	56	Normal		54	Survived
A-4	8.0	12	1,400	110	175	23.0	100	14.0	60	Normal		101	Survived
A-5	9.5	17	1,500	88	157	6.0	30	4.0	20	Edema		35	Survived
A-6	9.0	11	1,300	118	144	24.0	100	16.0	66	Normal			Death; unknown cause
A-7	8.0	12	1,000	83	125	20.0	81			Normal			Death; cardiac arrest
A-8	8.0	14	1,000	71	125	7.0	38	1.3	7	Edema	Hemorrhage Edema	2	Survived
A-9	8.0	10	850	85	106	17.0	81	6.0	30	Normal		39	Survived
A-10	9.0	14	1,300	93	144	17.0	86	11.0	54	Normal		22	Death; unknown cause
A-11	8.0	11	900	82	112	16.0	89	5.0	27	Normal		34	Death; cannula disconnected and dog exsanguinated
A-12	7.5	15	1,500	100	200	21.0	98	15.0	67	Normal			Survived; donor lung dextran flush

TALBE II. PERFUSION OF DOG LUNG WITH HUMAN BLOOD

NO.	DONOR WEIGHT	FLOW		LENGTH OF PERFUSION (MIN.)	VOLUME (ML.) AND TYPE OF PLASMA EXPANDER	RESIDUAL CELLS	TYPE OF ANTI-COAGULANT	PATHOLOGY	
		TOTAL ML./MIN.	ML./KG.					GROSS	MICROSCOPIC
B-1	10	760	76	30	Dextran 3,000	Trace	ACD Heparin	Normal	Widespread fibrin thrombi; perivascular hemorrhage
B-2	9	760	85	30	Dextran 2,000	None	ACD	Normal	Widespread fibrin thrombi; perivascular hemorrhage
B-3	11	760	69	45	Dextran 2,500	Trace	ACD	Normal	Atelectasis and rare fibrin thrombi in pulmonary artery branches
B-4	10	600	60	30	Dextran 2,000	None	ACD	Edema	Widespread fibrin thrombi; perivascular hemorrhages; edema
B-5	10	900	90	30	Dextran 2,000	None	ACD	Edema	Widespread fibrin thrombi; perivascular hemorrhages; edema
B-6	10	900	90	30	Dextran 3,000	Trace	ACD	Edema	Massive agglutination and hemolysis of RBC; fibrin thrombi; edema
B-7	11	1,200	109	20	Dextran 2,500	Trace	ACD	Edema	Rare fibrin thrombi in pulmonary artery; perivascular hemorrhages; edema
B-8	12	700	51	10	Dextran 2,500	Trace	ACD	Edema	Massive agglutination and hemolysis of RBC; rare fibrin thrombi in pulmonary artery; edema
B-9	10	Plasma 3,600 Blood 1,500	Plasma 360 Blood 150	Plasma 20 Blood 10	Dextran 2,000	Trace	ACD	Edema	Diffuse pulmonary edema and fibrin thrombi
B-10	8	1,000	125	10	PVP 4,500	Trace	ACD	Edema	Widespread coagulation; fibrin thrombi
B-11	10	200	20	10	PVP 4,500	Trace	Heparin	Edema	Diffuse pulmonary edema and fibrin thrombi; perivascular hemorrhages
B-12	10	200	20	10	PVP 2,500	Trace	Heparin	Edema	Diffuse pulmonary edema and fibrin thrombi; perivascular hemorrhages

PVP: Polyvinyl pyrrolidine.
Dextran: Plavolex.
Trace: RBC grossly visible only after centrifugation.
ACD: Acid citrate, dextrose 75 ml./500 ml. blood.

to be positive in 2. Blood cultures had been studied in earlier experiments and had been found negative when the described sterilization technique was used.

Perfusion of Dog Lung With Human Blood.—When human blood was perfused through similarly prepared dog lungs, 9 of 12 pairs of lungs showed severe edema which appeared within 5 to 10 minutes after start of the perfusion and was so abundant that flow would drop to 50 to 60 ml. per minute and nearly this much plasma would appear in the trachea. Perfusion thus often had to be discontinued after 10 minutes. We were never able to determine why the first 3 pilot experiments were not associated with pulmonary edema. These were done before the dog work mentioned above was begun and some months before the additional 9 experiments.

Particular care was given to flushing the lungs, and although all cells could not be removed as seen by microscopic study, the washed lungs were white and the perfusate was grossly clear. Edema was produced whether the perfused blood was citrated or was treated with heparin and was also noted when only plasma was perfused. Flow in some instances was never more than 200 ml. per minute through the lungs.

Microscopic examination showed widespread fibrin thrombi in the pulmonary arteries, and in the last 9 experiments there were massive perivascular hemorrhages and edema. The presence of fibrin thrombi without significant numbers of red cells suggested a tissue reaction between the dog lung and human protein independent of the red blood cells.

DISCUSSION

In contrast to the technique of others we did not remove the lungs from the donor's chest but rather siphoned blood from the left atrium. This was done to avoid manipulation and trauma to the lung in removing it and to avoid contact of blood with air except through a membrane. The good results with perfusion of homologous blood at 100 to 200 ml. per kilogram of donor body weight per minute suggest that this method is advantageous, as Campbell and associates[1] were able to perfuse only up to 800 ml. through the lungs of large mongrel dogs. Dog lungs used with the automatically controlled pump became a useful experimental method for extracorporeal oxygenation in the dog.

Our failure to perfuse human blood through dog lungs may have resulted from attempting to use too high a flow. We believe, however, that the desired extracorporeal oxygenator should oxygenate up to 100 ml. of blood per kilogram of body weight of the donor. Experiments with perfusion of homologous blood showed that the dog lung would more than meet this requirement. Human blood could not be so perfused in spite of a thorough flushing with plasma expander, nonpulsatile flow, and no increased pulmonary venous pressure. The widespread thrombi in pulmonary vessels of the dog lung perfused with human blood, even if no edema were evident, suggested a chemical incompatibility possibly inherent in the tissues of the lung itself. Hardaway and associates[3, 4] have clearly shown the incompatibility of human blood injected into the dog and the resulting intravascular clotting.

Several important by-products of this study deserve mention. Although some of our early experiments resulted in survival of the recipient, an appallingly high mortality rate followed. Pyrogens could be demonstrated in the perfusate by injecting it into rabbits.* When these were eliminated by careful washing and autoclaving of equipment at 270° F. for 30 minutes and the use of new tubing, there was a gratifying improvement in appearance of the dog, vasomotor stability, and survival rate.

The susceptibility of the dog to development of acidosis after operation was striking. This appeared unrelated to hypoxia during perfusion as the pH often fell only after the procedure was completed. Shock and oliguria exaggerated the acidosis; adequate blood replacement often improved it. The severe acidosis (pH to 7.00) seemed irreversible without aid to the recipient and sodium bicarbonate was effectively used intravenously.

CONCLUSION

The dog lung remaining in the chest but with vascular connections severed can be used as a good oxygenator for extracorporeal cardiopulmonary bypass in the dog.

Results with by-pass perfusion were strikingly improved by (1) elimination of pyrogens from tubing and solutions, (2) attention to and correction of acidosis after operation, (3) careful maintenance of blood volume, and (4) the use of broad spectrum antibiotics.

The dog lung does not appear sufficiently compatible with human blood to allow an adequate reserve of oxygenation and blood flow for clinical use.

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*These studies were done by Dr. Ivan Bennett and his associates.

ACTIVATION OF THE ANTERIOR PITUITARY BY CERVICAL SYMPATHECTOMY*

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THE cause of Simmonds' disease is generally regarded to be an insufficiency of the anterior pituitary. In this report, observations will be recorded pertaining to clinical results secured by cervical sympathectomy performed to activate a deficient anterior pituitary in patients with Simmonds' disease.

In 1913, Walter Dandy cited the importance of the cervical sympathetic innervation of the pituitary. Roussy and Mosinger[5, 6] showed that excision of the cervical sympathetic chains was followed by morphologic changes in the pituitary, namely, first, a vasodilatation and, second, histologic evidence of increased anterior pituitary activity. The pituitary receives inhibitory impulses as a result of sympathetic stimulation (inhibition of function because of vasoconstriction) and stimulating impulses from the hypothalamus (parasympathetic) which among other possibilities cause vasodilatation.

Histologic studies have revealed that the sympathetic fibers originate in the lower cervical and upper dorsal segments of the spinal cord, pass into the stellate ganglion, and course upward in the cervical sympathetic chain to the superior cervical ganglion where they synapse with fibers which continue to the pituitary via the pericarotid network.

EXPERIMENTAL

In 1936, at the suggestion of my former chief, the late Professor René Leriche,[4] and using the bioassay procedures of Aron in various sympathectomized patients, I observed that sympathectomy resulted in increased rental excretion rates of thyrotropic and gonadotropic hormones whenever these excretion rates were found decreased before operation, as, for example, in a patient with hypotension and asthenia. In other instances where preoperative secretion rates of pituitary hormones were normal, no postoperative changes occurred.

In association with J. Comsa[2] and using modern chemical analytical methods, I excised the superior cervical sympathetic ganglia in rats. Urine collections from individual rats were carried out and excretion rates of 17-ketosteroids and 11-oxysteroids for 24 hours were determined. The results may be summarized as follows. During the first 6 days after operation, there was an important increase in 11-oxysteroids, whereas the 17-ketosteroids decreased to

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Lecture delivered at the International University of Homburg (Sarre) before the Medical Staff of the American Medical Armed Forces in the Palatinate.

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below analytical levels. Of special note was the fact that such differences of excretion were noted in sham-operated animals as well, thus indicating that the changes are an expression of nonspecific reactions to surgery.

After the ninth day, the normal excretion rates again could be observed in sham-operated animals, but in the sympathectomized animals there was a markedly elevated excretion rate of 17-ketosteroids which persisted longer than one month (Figs. 1 and 2). Our interpretation of these facts is that in the sympathectomized animals the pituitary was stimulated and this in turn stimulated the adrenals.

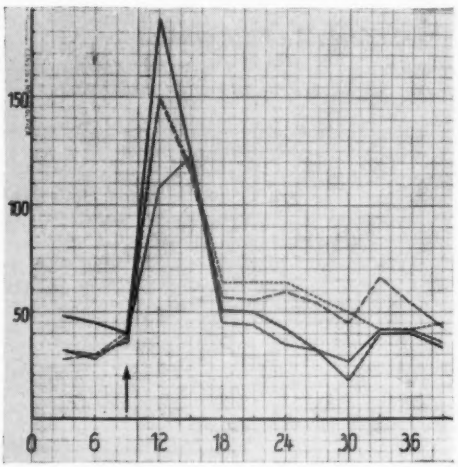

Fig. 1.

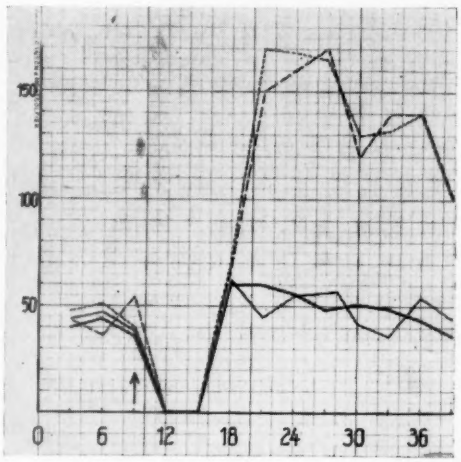

Fig. 2.

Fig. 1.—Urinary excretion rate of 11-oxysteroids in rats following extirpation of the right superior cervical sympathetic ganglion. Abscissa: time in days. Ordinate: 11-oxysteroids in gamma per 72-hour urine samples; determinations being continued during 39 days from individual experiments. Broken lines represent sympathectomized animals and solid lines represent sham operations in controls.

Fig. 2.—Urinary excretion rate of 17-ketosteroids in rats following extirpation of the right superior cervical sympathetic ganglion. Same notation as Fig. 1 (the ordinates indicate the 17-ketosteroids elimination rate in gammas in 72-hour urine samples, determination being continued during 39 days).

CASE REPORTS

The following are 3 case studies of patients with Simmonds' disease operated upon by cervical sympathectomy 10, 8, and 7 years previously, respectively, and followed during these periods. The earlier status of these patients was previously recorded.[3]

CASE 1.—M. A 48-year-old woman was first seen in 1946. During 3 previous years, her condition had been generally poor. She presented with complete loss of appetite, severe asthenia, and muscular atony. There had been loss in weight from 56 to 42 Kg. Her skin was atrophic and loose. Her teeth had become loose and 11 of 12 retained teeth had been extracted. Blood pressure was 95/65. Roentgenograms of the skull showed the sella turcica to be normal in shape but reduced in size.

The diagnosis of Simmonds' disease was made.

There was a rapid improvement in the patient's condition following injections of a crude extract of anterior pituitary gland. This persisted as long as the injections were continued, but her condition deteriorated when they were discontinued.

In October, 1946, both medial cervical sympathetic ganglia were extirpated through a transverse thyroid incision.

Anterior pituitary extract was not injected after the operation. She was discharged from the hospital on the eighth day. Her general condition improved rapidly. By the end of the second month she had gained 12 Kg.

She was seen again in June, 1956; her general condition was excellent.

CASE 2.—Mrs. B. 30 years of age, was first seen in 1948. Progressive general deterioration had persisted during the past 3 years. There had been loss of appetite, weight loss from 60 to 45 Kg., loss of teeth and hair, progressive asthenia, loose, dry, and pale skin and progressive amenorrhea.

Diagnosis was Simmonds' disease.

Transitory improvement was made by injections of anterior pituitary extracts. Injections of Novocain into cervical sympathetics afforded fairly satisfactory improvement in her general condition.

Each superior cervical sympathetic ganglion was removed at an interval of 10 days in September and October, 1948. Immediate general improvement followed these operations. The improvement was maintained as observed in 1949 and 1952. In 1953 there was some loss of appetite and weight, but these were again improved by general dietary measures. By the end of 1953, it was known that she was working regularly and was well.

CASE 3.—Mrs. S., 32 years of age, was first seen in 1949 in a state of profound general exhaustion. This began after her fourth pregnancy—this child was 3 years old at the time I first saw her. She complained specifically of headaches, loss of appetite, frequent vomiting, thirst, and polyuria. Blood pressure was 90/60. She had suffered amenorrhea and weight loss from 60 to 49 Kg.

During a year's time she received daily injections of anterior pituitary extract which afforded improvement.

Novocain injections into the stellate ganglia afforded a period of improvement.

In February, 1949, each superior cervical sympathetic ganglion was excised at an interval of 15 days. There was then noticeable improvement. The injections of anterior pituitary extract were discontinued. Improvement continued for only 2 months, and this was followed by resumption of injections of pituitary extracts. This case may be cited as a failure, yet she is still alive and able to carry out her usual household duties, receiving two injections of pituitary extract a week.

When last seen in June, 1956, she excreted 6.2 mg. of 17-ketosteroids and 0.7 mg. of 11-oxysteroids in the urine in 24 hours.

So far as the laboratory tests are concerned, the above observations seem incomplete. They were made during a period, 1946 to 1949, when the modern investigative methods (steroid analyses) were not possible in France. We had to rely upon clinical examination and clinical trial represented by the beneficial influences of anterior pituitary extract injection.

A similar attempt to activate the anterior pituitary has been recently successful in a case of adiposogenital dystrophy with cryptorchism.

It is known, indeed, that a pituitary deficiency is the main etiologic factor in cryptorchism in the great majority of instances and that gonadotropic preparations are beneficial in the therapy of this congenital condition.

The following is a summary of the case history.

CASE 4.—W. A., a boy of 9 years, was sent to us in November, 1955, for obesity, cryptorchism, and rather marked swelling of the jugular lymph nodes (Fig. 3).

Family history was negative.

He suffered from an undetermined intestinal disease at the age of one year. No other disease was noted until 1953 when he contracted successively almost every contagious disease of childhood (whooping cough, measles, chicken pox, and scarlet fever). In the meantime, a marked adenopathy appeared in the neck and lasted until the present. From this time (1953), the boy began to overeat, he grew fat, and his behavior became sluggish.

He was treated by different glandular preparations without noticeable success.

The boy, aged 8 when examined by us in November, 1955, was found to be obese and moonfaced. His skin was smooth and without any pigmentation of the external genital organs. The skin and hair appeared "baby-like." He was somewhat tall for his ago (127 cm. instead of the standard size, 122 cm.). He was considerably overweight (39.3 Kg. instead of standard weight, 23.5 Kg.) for his age. His fat was distributed more or less equally with predominance on the face, neck, and shoulders. Cryptorchism was present. The testes were not palpable and could not be pushed downward by massage of the inguinal cord.

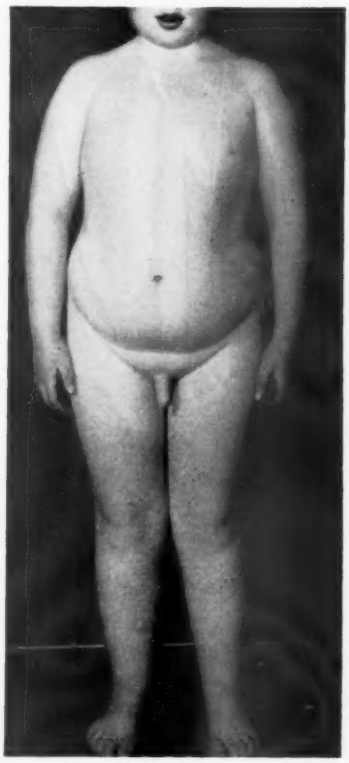

Fig. 3.—Boy of 9 years with obesity and bilateral cryptorchism. Weight 39.3 Kg. (standard, 23.5 Kg.); 11-oxysteroids and 17-ketosteroids urine excretions were noticeably decreased (see text). After bilateral operation (carotid sympathectomy with removal of the intercarotid corpuscle) both testes descended within 5 days after the operations. The rate of 11-oxysteroids and 17-ketosteroids became normal.

In the neck several large cherry-sized, mobile, discrete lymph nodes were present.

Both 11-oxysteroids and 17-ketosteroids were found noticeably decreased in the urine (Comsa): 11-oxysteroids, 120 gammas, and 17-ketosteroids, 200 gammas in 24-hour urine samples—which corresponds to about one-half of the rate found in infants aged 3 to 5 months and about 10 per cent of the normal rate for the boy's age.

Blood sugar was 115 mg. per cent. Basal metabolism was plus 12.1 per cent. Blood pressure was 11/7 and 13/6 cm. Blood cytology was normal.

The diagnosis of adiposogenital dystrophy was obvious.

Treatment: Urged by the parents to remove the jugular lymph nodes, we decided to perform at the same time a pericarotid sympathectomy at the origin of the internal carotid arteries.

Each side was operated upon at one month's interval (December, 1955, and January, 1956). The operation consisted of the removal of the adventitia and also the carotid bodies. The cervical lymph nodes also were extirpated; histologic examination showed some sclerosis without other specific alterations.

After the first operation the 11-oxysteroids were excreted in the urine at the rate of 780 gammas a day; 17-ketosteroids were 1 mg. a day (still deceased).

After the second operation 11-oxysteroids were 360 gammas daily (normal) and 17-ketosteroids were 1.96 mg. a day which is about the lower limit of the normal range.

It was noted that 5 days after the second operation both testes descended; the right one about cherry size was completely in the scrotum, the left one was smaller and remained at the external orifice of the inguinal canal.

When discharged, the boy was placed on a restricted diet of green vegetables and fruit. Under these conditions, he gained weight during the first 2 months—2 Kg. Later he lost 8 Kg. in 4 months.

In May, 1955, he weighed 31.3 Kg.; 11-oxysteroids were excreted at the rate of 580 gammas daily and 17-ketosteroids 5 mg. in 24 hours. Both figures are fairly normal for his age.

A dark pigmentation of the external genital organs was now apparent.

In conclusion, it is felt that cervical sympathectomy activated the anterior pituitary by causing at least a localized vasodilatation. It would be hard to assume a mere coincidence between the operation and the improvement in the patient's condition.

A word may be said concerning the types of cervical sympathectomy.

Three possibilities exist: (1) interruption of the cervical chain which, concerning the anterior pituitary, consists of an interruption of the preganglionic fibers; (2) resection of the upper cervical ganglia—the "ganglionic operation"—since these ganglia are the center of the vegetative functions of the anterior pituitary; and (3) periarterial sympathectomy of the internal carotid arteries which means suppression of retroganglionic fibers.

In principle all 3 are effective. The first two seem more effective, but the third has the advantage of not producing a Claude Bernard-Horner syndrome.

SUMMARY

1. We have shown that cervical sympathectomy in the rat results in an increased urinary excretion of 17-ketosteroids, which persists after 3 months.

2. Four clinical observations are reported:

a. Three cases of Simmonds' cachexia are presented. Two of those are improved 10 and 8 years, respectively, after extirpation of the superior or medial cervical sympathetic ganglia. In the third case a limited improvement was obtained.

b. A case of cryptorchism where the testes descended suddenly after bilateral pericarotid sympathectomy is discussed. This was accompanied by an increase of the urinary steroid excretion up to normal levels.

3. The operative procedures that could be employed for cervical sympathectomy to activate the pituitary are bilateral resection of the superior or medial sympathetic cervical ganglia or the unilateral or bilateral pericarotid sympathectomy. In principle, all 3 are sufficient. The first two seem more effective, but the third has the advantage of not producing a Claude Bernard-Horner syndrome.

4. Activation of hypofunctioning endocrine glands, particularly the anterior pituitary by sympathectomy is discussed. The mechanism for this would appear, at least in part, to be the induction of a local vasodilatation to increase blood supply.

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A NEW CONCEPT OF THE SYMPATHETIC PATHWAYS TO THE EYE

A New Technique to Avoid a Horner's Syndrome

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INTRODUCTION

MANY authorities and investigators in American texts and in current literature have defined the sympathetic pathways controlling the dilatation of the human pupil by the smooth muscles of the iris as existing as a specific pathway.[1-3, 5, 7, 9-13, 18, 20, 22, 23, 25] The establishment of these fixed pathway patterns resulted from dissection and clinical observation in the cadaver and at surgery.[10-12, 14-17, 21, 25, 26]

CURRENT ANATOMIC AND PHYSIOLOGIC CONCEPTS

On the basis of a composite analysis of the available material on this subject, it must be assumed that the cell bodies of the preganglionic neurons are located in the eighth cervical and first or second thoracic (dorsal) levels of the spinal cord. The greatest number apparently are present in the first thoracic segment. These preganglionic neurons leave the spinal cord mainly in the first and second thoracic ventral roots and enter the sympathetic chain at these levels via the rami communicantes. The majority of these pathways exist in the first thoracic ramus and pass through the first thoracic (dorsal) ganglion (Fig. 1, *A*).

These preganglionic neurons pass cephalad through the stellate ganglion, ascending in the sympathetic cervical chain to form a synapse with postganglionic neurons in the superior cervical ganglion. These latter fibers then pass via the carotid vessels or by way of the nasociliary nerves to the ciliary muscles, which control papillary action (Fig. 1, *A*). Stimulation of these fibers produces dilatation of the pupil; division or paralysis of these pathways results in a constricted (miotic) pupil.

Several authorities have indicated that occasionally the sympathetic pathways to the eye pass through separate paravertebral ganglia closely associated with the ventral roots of the eighth cervical, first and/or second thoracic nerves and that these preganglionic neurons do not enter the thoracic sympathetic chain but do enter it at the upper level of the stellate ganglion.[11, 14-18] This latter pathway pattern, according to these authorities, is not commonly found in man.[11, 18]

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CURRENT CONCEPTS CONCERNING PRODUCTION OF HORNER'S SYNDROME

Interference with these pathways outside of the central nervous system by disease, tumors, surgical division, or trauma usually results in a Horner's syndrome. This syndrome is unsightly and is characterized mainly by a constricted pupil (miosis), lagophthalmos with narrowing of the palpebral fissure, and enophthalmos. It has been reported by many that interruption of the ventral roots of the first and second thoracic nerves or removal of the lower portion of the stellate ganglion or the first and second thoracic ganglia resulted in a Horner's syndrome.[3, 5, 6, 8-12, 18, 20, 22, 23, 24, 26] Also, it has been shown that when the upper portion of the stellate ganglion is destroyed, a Horner's syndrome develops even though the lower portion is not disturbed.[25]

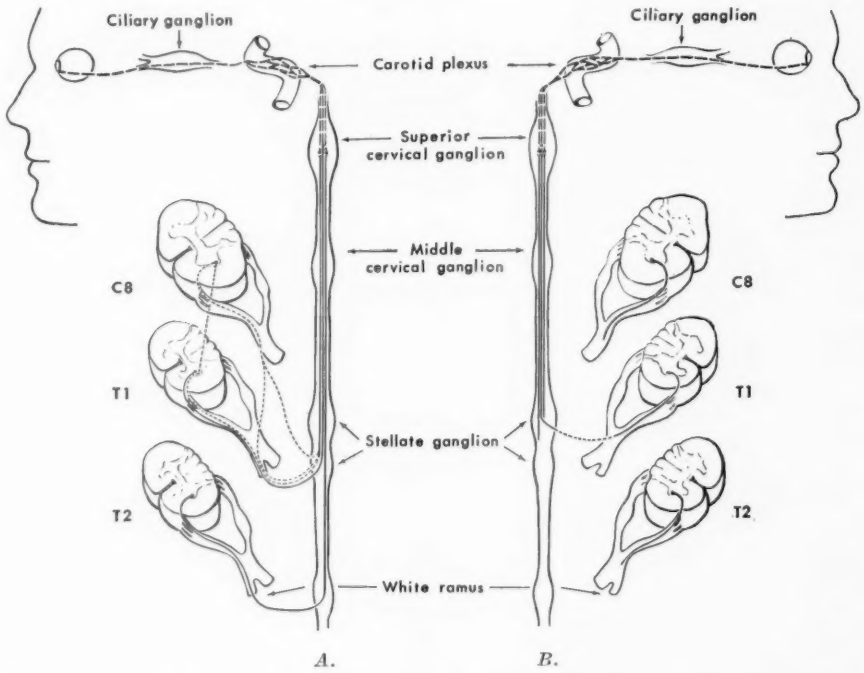
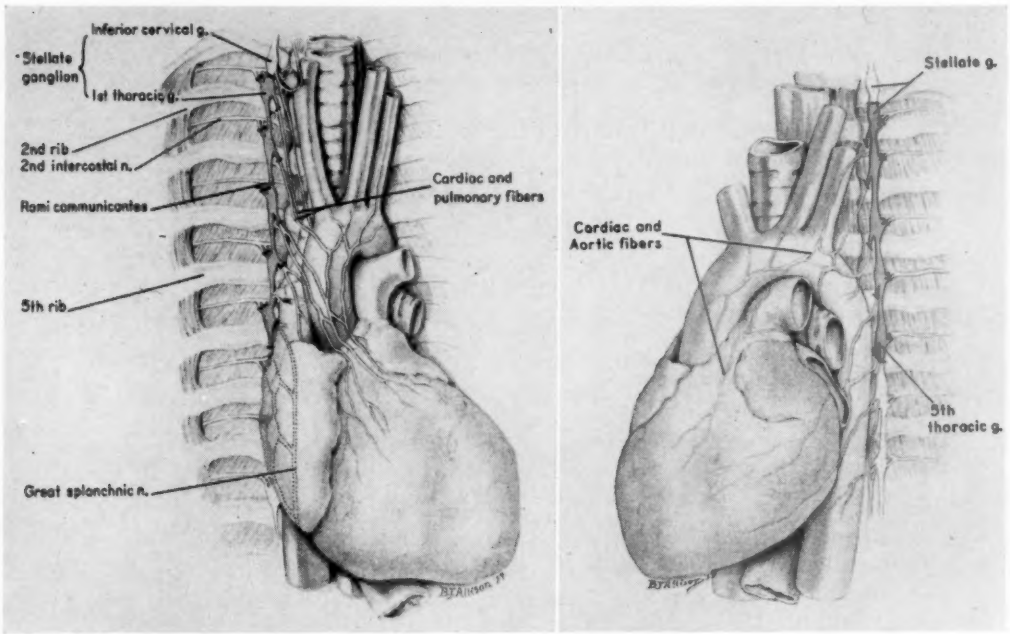


Fig. 1.—*A*, Pupillociliary pathways as recorded in the current literature and in texts as shown on left side with preganglionic neurons arising from the eighth cervical, first and/or second thoracic levels of the cord. They pass via the first or second ramus to enter the first dorsal ganglion. They then pass cephalad in the cervical sympathetic chain to synapse with postganglionic neurons in the superior cervical ganglion. *B*, As a result of our clinical studies, we postulate that the origin of the preganglionic neurons from the spinal cord is as shown in *A*; however, these fibers leave the ventral roots as shown in *B* and do not pass via the rami communicantes; they enter the upper portion of the stellate ganglion as shown on the right side of this drawing. The critical difference is that the pupillociliary pathways do not pass via the rami to the lower part of the stellate ganglion as previously recorded by other authorities, but apparently leave the ventral roots and pass by a separate paravertebral pathway to the upper portion of the stellate ganglion.

The stellate ganglion represents a fusion of the inferior cervical and first thoracic ganglia (Fig. 1, *A* and *B*). It lies at the base of the neck, anterior to the angle of the first rib; it extends from above the rib to a point midway between the first and second ribs. Variations exist in the size and extent as well as in the branches and communications to and from this ganglion as has been found by Sheehan[21] through careful dissection of this area in the adult cadaver.

SURGICAL PROCEDURES FOLLOWED BY A HORNER'S SYNDROME

Accordingly, if the sympathetic pathways as outlined above are interrupted at any point from their origin in the ventral roots of the eighth cervical, first and second thoracic nerves to their final point of innervation, then a Horner's syndrome would occur. Therefore, in the performance of an upper thoracic sympathectomy in which the inferior cervical ganglion, the first dorsal ganglion, and/or the upper dorsal rami are divided or resected, a Horner's syndrome should occur (Fig. 1, *A*). Furthermore, according to the data above and the results obtained by others, when only the rami to the first and second thoracic nerves and/or the first dorsal ganglion are resected, a Horner's syndrome should likewise develop.[3-7, 13, 18-20, 22-25]



A. *B.*

Fig. 2.—*A*, Relational anatomy of the heart, great vessels, the sympathetic chain, ganglia, rami, and associated branches as seen in a right thoracic exposure. The dark area of the sympathetic chain indicates the portion which is removed, and the short black bars indicate the sites where division of the rami and branches are accomplished. *B*, The same as *A* as seen from a left thoracic exposure. The point of transverse division of the stellate ganglion is clearly seen as being just cephalad to the first dorsal ramus in both figures, in order to avoid a Horner's syndrome. (Fig. 2, *A* and *B* courtesy Palumbo, L. T.: Anterior Transthoracic Approach for Upper Thoracic Sympathectomy, A. M. A. Arch. Surg. 72: 659, 1956.)

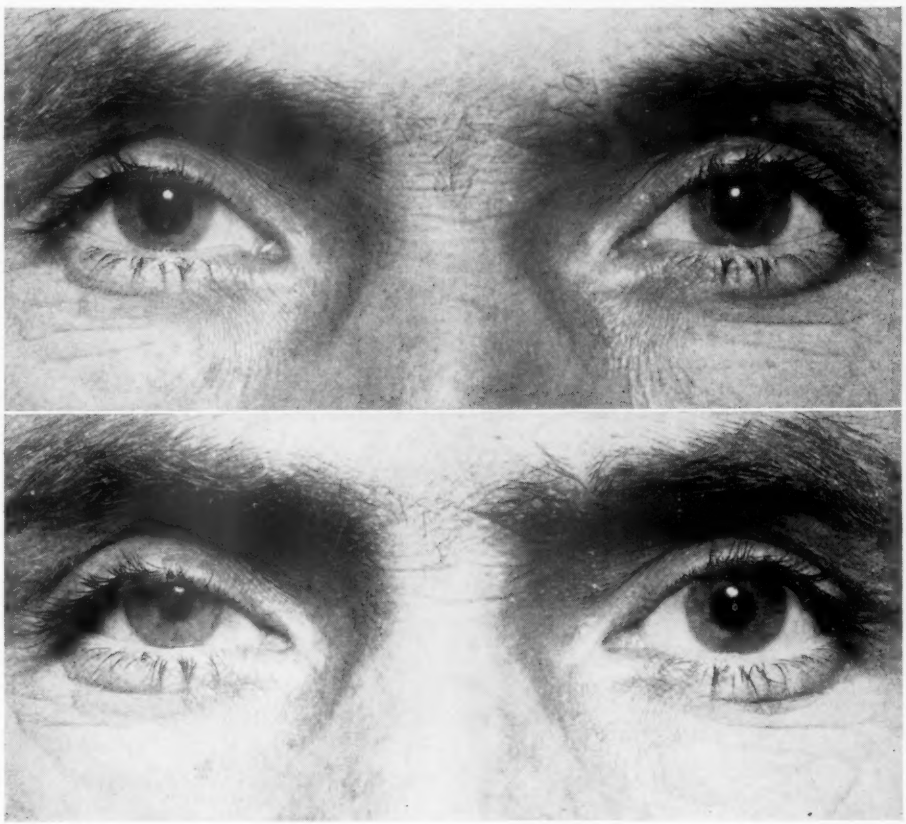
Contrary to this, our experience has shown that a Horner's syndrome does not occur if the rami from the first and second thoracic nerves and the upper dorsal ganglia including the first (lower one-third of the stellate ganglion) are divided and resected (Fig. 2, *A* and *B*). These findings followed the development of a new surgical approach to this segment of the thoracic sympathetics[14-17] which will be presented later.

With the excision of the sympathetic chain and associated ganglia from the fifth thoracic upward to include only the first thoracic (dorsal) ganglion just cephalad to the first thoracic *ramus communicans* and with the division of

all branches and communications coming to or from the chain in this segment, a Horner's syndrome can be avoided (Fig. 2, *A* and *B*). However, if the dissection of the stellate ganglion is carried cephalad to this first ramus or a higher resection of this ganglion is accomplished, a Horner's syndrome will occur.

Therefore, from our clinical experience of utilization of this technique in 49 consecutive upper dorsal sympathectomies with the extent of resection as shown in Fig. 2, *A* and *B*, we must assume that the pupillociliary sympathetic pathways do not transverse the first ramus communicans to enter the first thoracic (dorsal) ganglion (lower part of stellate ganglion) as previously

A.



B.

Fig. 3.—*A*, Pupils equal and regular prior to sympathectomy. *B*, Horner's syndrome on patient's right (narrowed palpebral fissure, miotic pupil) followed overmobilization of the right stellate ganglion during upper thoracic sympathectomy. No change in left pupil following upper dorsal sympathectomy by the technique as described in this presentation.

recorded by authorities in this field. Apparently, these fibers leave the ventral roots of the eighth cervical, first and/or second thoracic nerves passing via a separate paravertebral pathway to gain entrance to the upper aspect of the stellate ganglion (Fig. 1, *B*). If the dissection is carried above the first ramus to include a more extensive mobilization of the stellate ganglion, as performed

in two cases in our series, a Horner's syndrome will occur (Fig. 3, *A* and *B*). This is corroborative evidence that these pathways enter at a higher level in the stellate ganglion and not at the first thoracic ganglion (Fig. 1, *B*).

NEW SURGICAL TECHNIQUE TO AVOID HORNER'S SYNDROME

For many years, the various techniques and surgical approaches advocated for sympathetic denervation of the upper extremities, head, neck, and/or heart, and coronary vessels left much to be desired. Particularly was this true with respect to the indirect and difficult surgical approach thus provided to this segment of the sympathetic chain. In addition, the results were frequently only partially successful due to the incompleteness of the sympathetic denervation. The merits of the indications and details of the technique employed in this series have been published elsewhere.[14-17]

A.

B.

Fig. 4.—*A*, Pupils equal and regular prior to sympathectomy. *B*, Pupils remain equal and regular following left upper dorsal sympathectomy by the technique described in this presentation.

Since April, 1953, we have employed a new surgical approach to the upper thoracic sympathetic chain consisting of an anterior transthoracic, transpleural incision through the third intercostal space. This provides a quick, easier direct

attack upon this segment of the chain. It allowed a more meticulous and careful dissection of this area, permitting the surgeon ample room under direct visualization of the structures. Any variations in the anatomic structures can thus be easily recognized and the procedure modified accordingly. As a result of the careful dissection this exposure has consistently allowed, clinical observations in our series strongly indicate that the current concepts are incorrect concerning the point of entry of the sympathetic pupillociliary pathways into the sympathetic chain.

In 45 operations in which our technique was carefully performed, a Horner's syndrome did not occur (Fig. 4, *A* and *B*). However, in 2 cases in which deviations from the technique were necessary, a Horner's syndrome did occur. In the first case, existing pathology forced a more extensive dissection and in

A. *B.*

Fig. 5.—*A*, Typical complete loss of sweating bilaterally and anteriorly of head, neck, shoulder, chest, and upper extremities following upper dorsal sympathectomy. (Light areas represent loss of sweating by Minor's starch-iodine technique.) *B*, Typical complete loss of sweating posteriorly.

the other a higher dissection was necessary to demonstrate the entire stellate ganglion. In each case, a permanent Horner's syndrome resulted on that side (Fig. 3, *A* and *B*). When these 2 patients came to operation for the opposite sides, the same technique and resection as employed for the other 30 operations was possible and a Horner's syndrome did not occur (Fig. 3, *A* and *B*). In the third case, a bilateral Horner's syndrome developed; this may represent variants in the sympathetic pathways.

The typical loss of sweating of the areas of the head, neck, shoulder, upper portions of the chest, and upper extremities anteriorly and posteriorly is shown in 2 cases (Figs. 5 and 6). Since sweating normally results from stimulation of the sympathetics and can be permanently eliminated following adequate interruption of these pathways, the Minor starch-iodine method is an excellent way to visualize the extent and permanence of the sympathetic denervation.

A. *B.*

Fig. 6.—*A*, Anterior view with typical left unilateral loss of sweating of head, neck, thorax, and upper extremities. Healed incision visible below left nipple. *B*, Posterior view with typical loss of sweating in left side.

CLINICAL APPLICATION

This method and extent of sympathetic denervation has a broad clinical application. It is indicated and beneficial in a variety of diseases and conditions as listed in Table I.

TABLE I. UPPER DORSAL SYMPATHECTOMY VALUABLE IN—

Angina pectoris	Coronary heart disease
Peripheral arteriosclerosis	Acrocyanosis
Raynaud's disease	Scleroderma
Buerger's disease	Sudeck's atrophy
Causalgia	Chilblains
Frostbite	Hyperhidrosis
Shoulder-hand syndrome	Carotid sinus syndrome
Paroxysmal tachycardia	Phantom limb
Thrombosis of major vessels	Erythromelalgia
Arteriovenous fistula and aneurysm	

SUMMARY

The sympathetic pupillociliary pathways controlling the dilatation of the pupil in the adult human have been recorded by many authorities as passing via the first and/or second thoracic (dorsal) rami to the lower part of the

stellate (first thoracic) ganglion. It has been stated by these and other authorities that the removal of the lower part of the stellate ganglion and/or resection of the first and/or second thoracic rami would produce a Horner's syndrome. This currently accepted concept of the sympathetic pathways to the human adult eye we believe to be incorrect.

Our entire clinical experience has consistently contradicted the findings and reports of other investigators. It is suggested that the ability afforded by a new surgical approach to reach, dissect, and exactly control the line of resection without undue trauma to the stellate ganglion has made possible for the first time a definitive statement concerning the entry of the pupillociliary pathways into the sympathetic chain.

It is, therefore, postulated that the preganglionic neurons controlling the pupil enter the upper portion of the stellate ganglion by a separate paravertebral route leaving the ventral roots of the eighth cervical, first and/or second thoracic nerves. Our entire clinical experience refutes the concept that these pathways pass via the first ramus communicans to the first thoracic ganglion.

This thesis is based on and supported by the results of a new surgical approach originally designed to permit a more direct exposure and to overcome many of the deficiencies of current surgical approaches.

The anterior transthoracic, transpleural wound employed allows a more direct approach and a more accurate and complete dissection of this segment of the sympathetic supply to the head, neck, upper extremity, heart, and coronary vessels without incurring the undesirable sequela of a Horner's syndrome.

I wish to give grateful acknowledgment to Dr. Harry Samberg, Chief, Physical Medicine and Rehabilitation, and his group for their work with sweating patterns.

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Editorial

Conducted by I. S. Ravdin, M.D.

Medical Education and the Shades of Gray

In the main, the primary function of our schools of medicine is to prepare the student to be a competent physician. Upon graduation he may or may not choose to practice, as the scope of Medicine is broad and a variety of opportunities are available, should he find another facet more to his liking. His medical school experience should be an educational enterprise which prepares him sufficiently to elect to do as he wishes after graduation: general practice, specialty training, teaching, research, or any of their combinations. It is probably best that his educational background in Medicine be broad and with no great emphasis upon a particular end other than competence. In this sense the functions of Medical Education resemble those of the college granting the Bachelor of Arts degree. Technical details, while eventually very important, probably should be left largely to the years of internship and residency training.

Can these "Aims in Education" be achieved in medicine without the introduction of disadvantages that may outweigh any gains such an approach might have? Perhaps they can if we examine carefully a number of existing problems. A major one is the need to delineate, when possible, educational and training values. Often both are involved simultaneously, though frequently differing in degree. In medical school the chief emphasis should be an educational one; the internship and residency years are primarily for training with application of knowledge and the marshaling of experience being the prime concern.

The student whose medical school years leave upon him the mark of essentiality for continued self-education, continued reading, and the cultivation of thoughtful criticism and evaluation gives us little concern for his ultimate future. He is also likely to be a better citizen in his community and a better ambassador for our profession. He needs to continue to be a student for his own protection, as well. His attitudes and mind need to remain adaptable to the newer developments in Medicine, if he is not to be unduly penalized by the changes constantly taking place.

The extent to which we succeed or fail in medical education in large measure depends upon two considerations: first is the selection of the college students to enter Medicine; second is the atmosphere and substance to which the student is exposed during his years in medical school. It is impossible to turn out quality students if quality students are not admitted. An excellent student generally

continues his excellence in any school, although he may be a better physician if his medical school experience has been a good one. The handicaps imposed upon the faculty by the student of poor quality are difficult if not impossible to be overcome. The poor student may improve a little should he be exposed to a school higher in quality than his college record warrants admission. Yet, academic performance is not the only indicator of success in later years; exceptions are outstanding and fairly commonly encountered, for the student's ability to achieve the confidence of his patients and colleagues, to translate theory into practical action, his personal habits, and the integrity of his everyday life are among the important qualities having a bearing upon his success in practice that may not have been fairly tested during his years of schooling. These can overcome the handicaps of a modest academic record, particularly if he continues to study.

One wonders if there is enough which is unique in Medical Education to merit its special consideration apart from the principles of education in general. Methods of teaching in either instance are problems in techniques that generally concern the individual more than the school or its curriculum. Although the subject matter plays a role in the selection of the methods best suited for clear exposition, there is no one method best for all. The training of the teacher deserves some consideration apart from his education or qualifications, but the current trend seems to be away from methodology in favor of better grounding in the subject matter to be taught. The studious attitude of the teacher is best acquired by self-cultivation. Some of the techniques in teaching can be acquired by demonstration, more by experience. By and large, the teacher will adopt those methods best suited to him. In general, our methods of teaching are of no great consequence, provided they do not quench the appetite for learning nor direct attention from the central purpose of Medical Education. The stature, competence, and enthusiasm of the teacher in his subject matter are likely to have a greater influence upon the student than the details he may try to cover.

The teacher serves principally as the translator of cumulative knowledge. In this function, he can seldom avoid the bias of his own experience which understandably may impose rather specific values when a general emphasis might be more desirable. This is no great fault and may, in fact, be an important asset. The bias of experience, however, does point up the need for exposing the student to more than one teacher engaged in the same subject matter. A teacher without some bias is likely to be a reader and largely incapable of leading discussions or of teaching by example to depths greater than those which can be achieved by the student reading for himself.

When we teach, what should we emphasize, facts or principles? The latter are generally more useful, as facts are continuously in need of revision. Principles remain unchanged. Consider but two examples. The Periodic Table of the Elements, conceived by Mendeleeff and Meyer nearly 90 years ago, was an expression of physical principles formulated from the facts available in that day. With the passing of each decade, many new facts were added, and a

number of the older ones had to be changed, modified, or deleted as incorrect entirely. Had the 1870 table depended upon the facts of 1870, it probably could not have survived 15 years. The same can be said of the principles set forth by Harvey in his *De Moto Cordis* of 1628. These remain undisputed even today. Harvey did not need to see the capillaries to know that his principles were sound; his medical education at Padua did not include training in the use of the then available compound microscope and he did not live to see proof of their actual existence. The demonstration of such arteriovenous communications was poorly identified by the scholarly Malpighi in 1661 but excellently described a few years later by the untutored van Leeuwenhoek. It remained for the inquiring theologian, Stephen Hales, to recognize the significance of blood pressure to blood flow, and for Servetus (75 years before Harvey) to describe the cardiopulmonary circuit. Only within the past 60 years has the principle of the dependence of metabolism upon the circulation been generally recognized. All of these contributions are principles. Most of the facts in the era of their establishment have subsequently changed or have been refined. So rapidly do facts change, that the student, who has been nourished on facts instead of principles while in medical school, could put up a pretty good argument a decade or two later that he should be entitled to a refund on his tuition!

The criticism by educators is often voiced that the doctors often show no cultural interest beyond that of the profession. In some instances, this may be valid. If valid, wherein lies the fault? The years in medical school, of necessity, are assigned to the study of human biology and disease. There is substantial doubt that this is the time for the presentation of formal courses in humanistic subject matter.

Today the trend in some quarters is to enlarge the cultural background of the medical student. On the surface, this seems desirable. How? There is the suggestion that humantistic subject matter be continued into the medical curriculum. This is an interesting thought and may be worthy of limited exploration. But it would be surprising if such material would compete adequately for student interest at a time when his interests and drives center about the subjects basic to his professional career. Is this not desirable?

We tend to overlook the cultural value of science itself. There is something strangely paradoxical about an emphasis on the pleasures entailed in the reading and the discourse of the humanities whose cultural heritage is neither less nor more than that of the sciences; both are interrelated as well as interdependent. The troughs and crests of each have been largely superimposed throughout recorded history.

General Education, during the college and precollegiate years, has its opportunity to teach humanistic matter in whatever concentrations it may choose. Is it, then, the responsibility or the premise of Medical Education to assume the functions of the college of liberal arts when its own curriculum is already overcrowded with its own subject matter? If our Medical Education produces men whose three dimensions fail to include more cultural matter, should we encroach upon the fourth—that of time? This is our most precious item and what we seek to save.

Perhaps we should first review our policies on student selection for admission to our schools of medicine. If we wish our physicians of the future to be men of great perspective and broad in cultural background, then we should seek to admit to Medicine those students who have displayed such interests during their earlier years. In doing so, however, we may accomplish less than we hope, substituting one deficiency for another—one of greater consequence, that of an adequate interest and background in Medicine itself. Certainly the student must also be qualified as a potential scientist, well aware of the scientific method, and capable of caring properly for his patients.

In Education, there is little that is black or white; most remains as shades of gray.

—J. Garrott Allen
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Chicago, Ill.

Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

THE MEDIAN STERNAL INCISION IN INTRACARDIAC SURGERY WITH EXTRACORPOREAL CIRCULATION: A GENERAL EVALUATION OF ITS USE IN HEART SURGERY

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A COMPLETE vertical division of the sternum was used by Milton[3] in 1897 in an attempt to explore the posterior mediastinum. The incision has been used sporadically for a variety of purposes since that time. It has usually been considered of use in an approach to the pericardium for its resection. Holman and Willett[1] used incomplete vertical sternotomy with transection at the second intercostal space for pericardectomy. It has been applied also to removal of noncardiac lesions of the anterior mediastinum, such as a substernal thyroid adenoma. No thought was given to the sternal approach for ligation of patent ductus and coarctation surgery. The development of more advanced forms of cardiac operations was initially of procedures, such as mitral commissurotomy, which are best approached through the pleural cavity, usually the left. Intracardiac surgery requiring approach to the heart chambers through the left atrium or left ventricle would be inappropriate for sternal approach because of the posterior position of these structures.

Surgical procedures on the great vessels at or near their origins, those requiring approach through the right atrium, and those done through a right ventricular incision are all best approached from the front. Two choices of incision are available for such an anterior approach. One is the widely used transverse bilateral thoracotomy and the second is the vertical median sternotomy. Shumaker[5] reported use of the vertical incision for pulmonary valvulotomy, and Blalock[4] used it for the same lesion in some of his initial cases. Probably because the transverse incision follows the pattern of more familiar conventional incisions it is the choice of most workers in the field. A transverse incision provides complete exposure of the venae cavae in operations requiring their temporary occlusion or drainage to a pump-oxygenator. It also affords approach to the subclavian vessels for intubation for return flow from a pump-oxygenator. The vertical incision provides the same access.

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USE IN AORTIC AND PULMONARY VALVULOTOMY

We have reported the use of the vertical sternal incision in the approach to aortic and pulmonary valvulotomy under hypothermia.[2] The valves were visualized through the aorta and pulmonary artery during inflow occlusion. The advantages were immediately obvious. Without any sacrifice of exposure, its use avoided the trauma of the transverse incision and the cramping of the right thoracotomy incision. We have now used the incision in a total of 31 operations during hypothermia and inflow occlusion; 19 were transaortic valvulotomy, 9 were transpulmonary artery valvulotomy, and 3 were transventricular infundibular resection. Various advantages of the method have been observed.

The marked reduction in operating time was immediately noted. At least 40 minutes were saved in comparison to the time required to open and close the bilateral thoracotomy incision. Diminished trauma to the lungs is an obvious attribute of the incision. Neither pleural cavity need be opened except inadvertently if the pleurae overlap in the midline or purposely at the end of the procedure if intrapleural drainage is needed.

The blood pressure fall almost always observed during bilateral opening of the chest is much less marked. Some fall does occur due to loss of the negative phase of mediastinal pressure and its function in venous cardiac return.

Exposure of the great vessels, the right ventricle, and the right atrium is excellent and is facilitated by the absence of the awninglike upper and lower wound edges which characterize the transverse incision. The intrapericardial isolation of the superior vena cava for encirclement with tape is simpler than with other incisions.

For longitudinal incisions in the aorta and pulmonary artery, the incision is well orientated. The clamps which are placed on the edges of the arteriotomy wound for the purpose of allowing restoration of circulation during repair of the vessel lie in the axis of the incision and are well out of the way. At the same time the enclosed troughlike character of the wound is well suited to filling with saline to exclude air from the vessels before application of the clamp.

USE IN OPEN CARDIOTOMY WITH THE PUMP-OXYGENATOR

The application of this incision to intracardiac operations using the artificial pump-oxygenator for total cardiac by-pass provides for even more important advantages in ease of approach and avoidance of complications.

The principal sources of complications of cardiac by-pass with the pump-oxygenator have been those pertaining to the nervous system, pulmonary complications, and the complications arising in the heart. Problems of acid-base balance arising during artificial respiration have also played a part in the difficulty of the field.

The pulmonary complications of intracardiac surgery fall into several groups. Some are in common with all other types of surgery: atelectasis, pleural transudation, pneumonitis, and embolism. A major group is based on the pulmonary vascular changes which have been brought about by the underlying cardiac pathology as in mitral stenosis. Another group is related to

pulmonary hypertension due to cardiac defects which cause a continuous excess of pulmonary circulation, notably interventricular septal defects, but also including interatrial septal defect and patent ductus arteriosus. Also to be included in this group are the complications which can be imagined to be present in lungs which during their entire development have been deprived of a normal volume of pulmonary circuit flow. The cardiac lesions which can be considered to produce this effect are tetralogy of Fallot and interatrial septal defect with pulmonic stenosis. The lack of volume and, presumably, of development of the pulmonary vascular tree causes the anemic lung fields seen in a plain chest x-ray and in the visualization resulting from an angiocardiogram.

The final group of pulmonary complications are those which may be said to arise from the thoracotomy. These are largely dependent upon the initial development of atelectasis and are distinctly increased in incidence and severity by lung compression, manipulation, and collapse during surgery and the pain-chest splinting reaction of the patient following surgery.

The maximum length transverse bilateral thoracotomy widely utilized for intracardiac operations with the pump-oxygenator provides for the greatest possible augmentation of the group of pulmonary complications arising from all of these factors. Patients of the cyanotic group and those having pulmonary hypertension due to pulmonary vascular changes provide the highest mortality. In the cyanotic group intracardiac repair results in the immediate increase of the right heart output to normal into a vascular bed which is patently underdeveloped. In patients with pulmonary hypertension secondary to their defect the pulmonary vascular bed has become inadequate for normal flow because of arteriolar changes. The pulmonary trauma incident to the transverse bilateral incision used to repair these cases very logically may be considered to amplify the already present pulmonary disability.

In an attempt to avoid pulmonary complications and the trauma incident to the transverse incision in intracardiac surgery with the pump-oxygenator we have used the longitudinal sternum-splitting incision in 4 cases. The employment of this incision in the previously mentioned 31 cases of cardiac procedures requiring vena caval isolation for cardiac inflow occlusion provided the experience required for this more advanced application.

In no instance in the inflow occlusion–hypothermia group was any difficulty encountered in isolating the superior or inferior vena cava. It was repeatedly noted that the region of a possible persistent superior vena cava on the left side was easily accessible. In the most recent cases of this type of operation for pulmonic stenosis or aortic stenosis, the region of a possible patent ductus arteriosus was explored through the anterior mediastinum and found to be accessible without great difficulty. The anterior position of the outflow tract of the right ventricle was an obvious observation. In one patient, an instance of pulmonic stenosis with atrial septal defect, the right atrium was explored digitally after the stenotic valve had been corrected. Although the defect found was of foramen ovale origin and very small, it could have been repaired through the incision if it had been necessary.

As in operations not using the pump-oxygenator, the patient is placed on his back on the operating table, and a vertical, midline incision is made extending from an inch above the sternal notch to a point 2 to 3 inches below the xiphoid (Fig. 1). The skin incision may be varied by a transverse limb at the third intercostal space to diminish the visible scar. The linea alba of the upper abdomen is incised through the lower part of the incision without entering the peritoneal cavity. The sternum is incised using the Stryker saw. Holman mentioned use of a power saw for the sternum. It is apparently entirely safe as no instance of even minor damage to the mediastinal viscera has been observed in the total 35 cases. The incision is carried upward a short distance into the deep cervical fascia and the interclavicular ligament formed by fibers of the superior sternoclavicular ligament from each side must be transected. If the thymus is well developed, it is elevated from below or divided to complete the exposure of the superior portion of the pericardium. The left innominate vein appears during the dissection and is protected from injury. The pleural reflections of each side are easily identified and the pericardium is opened between them. After introduction of a suitable retractor, suspension sutures holding the edges of pericardium up to the wound edges are very useful.

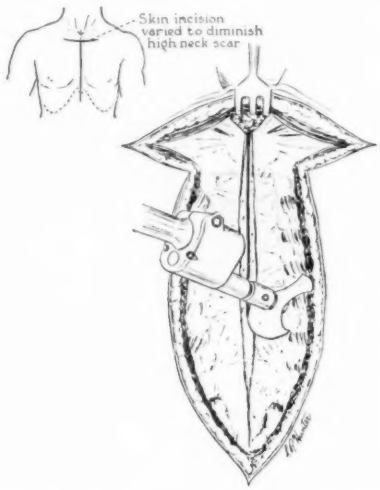


Fig. 1.—Skin incision is shown in modified T form used to minimize scar. Use of power of oscillating type is recommended.

The superior vena cava, within the pericardium and therefore below the azygos vein, may be encircled with the usual constricting tape most easily if a small nick is made in the pericardial reflection over the right pulmonary artery behind it. A curved clamp then passes behind the cava from the medial side to appear laterally under the edge of the vein within the pericardial sac. The inferior vena cava is entirely covered with serous pericardium which envelops it leaving a mesentery of pericardium behind or dorsal to it. The vein may be lifted and palpated by encircling fingers while a curved instrument passes behind it perforating this mesentery.

No difficulty is attendant to passing outflow catheters through the wall of the right atrium into the superior and inferior venae cavae in the usual manner.

The arterial inflow from the pump-oxygenator has been delivered to the systemic arterial system in our 4 cases through a segment of homologous artery anastomosed to the ascending aorta (Fig. 2). If the aorta is expected to be very small, the return flow might well be directed through a catheter introduced through a femoral artery. Great satisfaction was attendant to the use of a temporary side-arm graft, which follows the method though not the position described by Dodril because of the wide aperture and diameter of the return arterial tubing. In each case a plastic adapter of a size equal to the pump tubing was simply introduced as a cannula and tied into the side arm. The possibility is avoided of a suction effect on the cerebral and coronary flow which might be developed when a straight catheter is passed in a downward direction into the aorta through the left subclavian artery. Removal of the side arm at the completion of the procedure is neither difficult nor hazardous. In one of the cases a rim of the graft was left in place to facilitate suture.

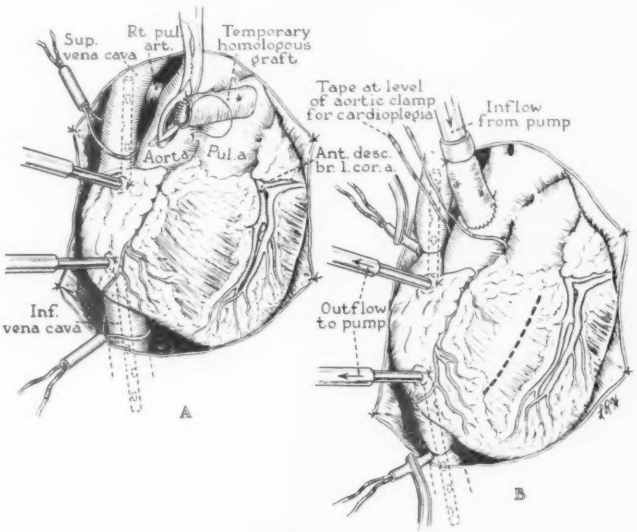


Fig. 2.—Diagrammatic representation of the central connections to the pump-oxygenator.

The sternum wound is securely closed with wire sutures placed either through drill holes in the bone or around the entire body of the sternum at rib interspaces. The solidity of the closure is important because it completely immobilizes the chest from abnormal movements and renders the postoperative period more comfortable. The security of wire sutures is essential. This was exemplified by our Case 2 in which death was due to wound disruption at the twelfth postoperative day. The sternum had been closed with absorbable sutures.

CASE REPORTS

The following cases illustrate the use of the vertical sternum-splitting incision.

CASE 1.—A 24-year-old man showed chronic hypotension, severe fatigue, and dyspnea on bed rest activities following a crushing chest injury sustained in an automobile accident.

Examination of the heart showed a new systolic murmur over the entire precordium most intense in the fourth left intercostal space at the sternal border. Cardiac catheterization through the superior vena cava confirmed the clinical impression of acquired, traumatic interventricular septal defect. The shunt was 11.71 L. per minute. The mean pulmonary arterial pressure was 44 mm. Hg.

Operation was performed through a median sternal-splitting incision 4 months after the injury. The usual caval outflow connections were made and the arterial inflow from the machine was through a homologous thoracic arterial segment. The side arm was connected by a simple over-and-over suture to a longitudinal incision in the ascending aorta of the patient made in a portion of the vessel excluded with a curved-toothed clamp. The end of the side arm was cannulated to connect to the one half-inch tubing leading from the machine. Potassium ion cardiac arrest was induced with potassium citrate injected into the aortic root proximal to a clamp applied to the aorta proximal to the side arm. Perfusion at a rate of 45 c.c. per kilogram was carried out for 27 minutes during which time right ventriculotomy and repair of a 2 by 4 cm. tear in the muscular portion of the septum was carried out. The repair was quickly done and the relatively prolonged perfusion was due to a brief period of ventricular fibrillation which ensued when the potassium cardiac asystole was relieved by allowing perfusion to reach the coronary ostia.

The monitoring electroencephalogram showed no change in the cerebral electrical activity during the operation and the patient recovered consciousness promptly. Six hours postoperatively a severe bradycardia and hypotension occurred and the patient became unresponsive, a state which did not improve with restoration of a good cardiac rate and normal blood pressure. He died on the fifth postoperative day without recovering consciousness. Autopsy showed a completely repaired defect in the septum and no changes in the brain adequate to explain anatomically the patient's course.

Case 2.—A 4-year-old boy with tetralogy of Fallot was subjected to surgery because of a marked and uncontrollable polycythemia. In spite of his age the Stryker saw was found to be a distinct aid in opening the chest through the sternum. The relatively large aorta was an ideal site for the implantation of the side-arm graft. In this case the graft selected was an adult common iliac artery which very closely approximated the one fourth-inch cannula of the tubing system. During 18 minutes of perfusion a diaphragmatic infundibular obstruction was removed and the high septal defect repaired using interrupted sutures tied over an Ivalon sponge pledget. The heart recovered from the potassium ion arrest spontaneously before the aorta clamp had been removed because of the very large bronchial flow which drained into the left ventricle in adequate amount to clear the coronary system of the arresting ion. The ventriculotomy was closed with the heart in sinus rhythm. The patient was awake at the conclusion of the operation and despite a severe hyponatremia followed a favorable early course. The absence of pulmonary complications or difficulties was striking. Disruption of the chest incision on the twelfth postoperative day led to infection and death.

Case 3.—A 7-year-old white girl was known to have had a heart murmur since birth. In early childhood she had frequent upper respiratory infections associated with cyanosis. In recent years the cyanosis had not occurred but the child suffered attacks of syncope associated with exercise.

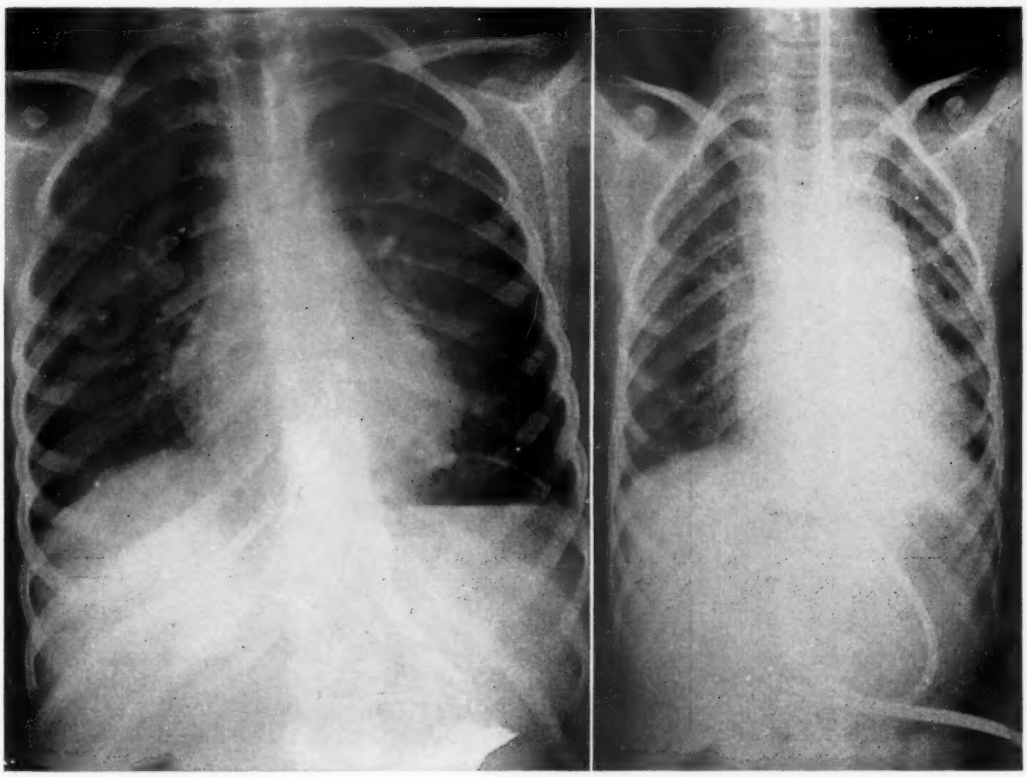
A harsh systolic murmur could be heard best at the fourth intercostal space just to the left of the sternum. There was no clubbing. Cardiac catheterization confirmed the clinical impression of interventricular defect. The right ventricular systolic pressure was 63 mm. Hg with an end diastolic pressure of 9 mm. Hg. The pulmonary artery mean pressure was 44 mm. Hg.

Through a median vertical sternotomy incision the cavae were encircled with tapes and outflow catheters introduced without entering either chest cavity. A segment of homologous graft was then anastomosed to the side of the ascending aorta and the inflow catheter attached. After heparinization the extracorporeal flow was instituted and potassium ion cardiac arrest instituted. Through a right ventricular cardiotomy wound a defect in the

posterior portion of the interventricular defect was closed with 4 interrupted 2-0 black silk sutures. As the cardiotomy wound was being closed ventricular fibrillation ensued. Normal rhythm was immediately re-established by electrical stimulation.

The sternum was approximated with 7 stainless steel wire sutures. A catheter drain was placed in the mediastinum and brought out through a stab wound in the skin of the upper abdomen.

Recovery was prompt and uncomplicated. The child was discharged on the seventeenth postoperative day. The condition of the chest was followed by x-rays which showed little change in lung or mediastinum at any time (Fig. 3).



A. *B.*

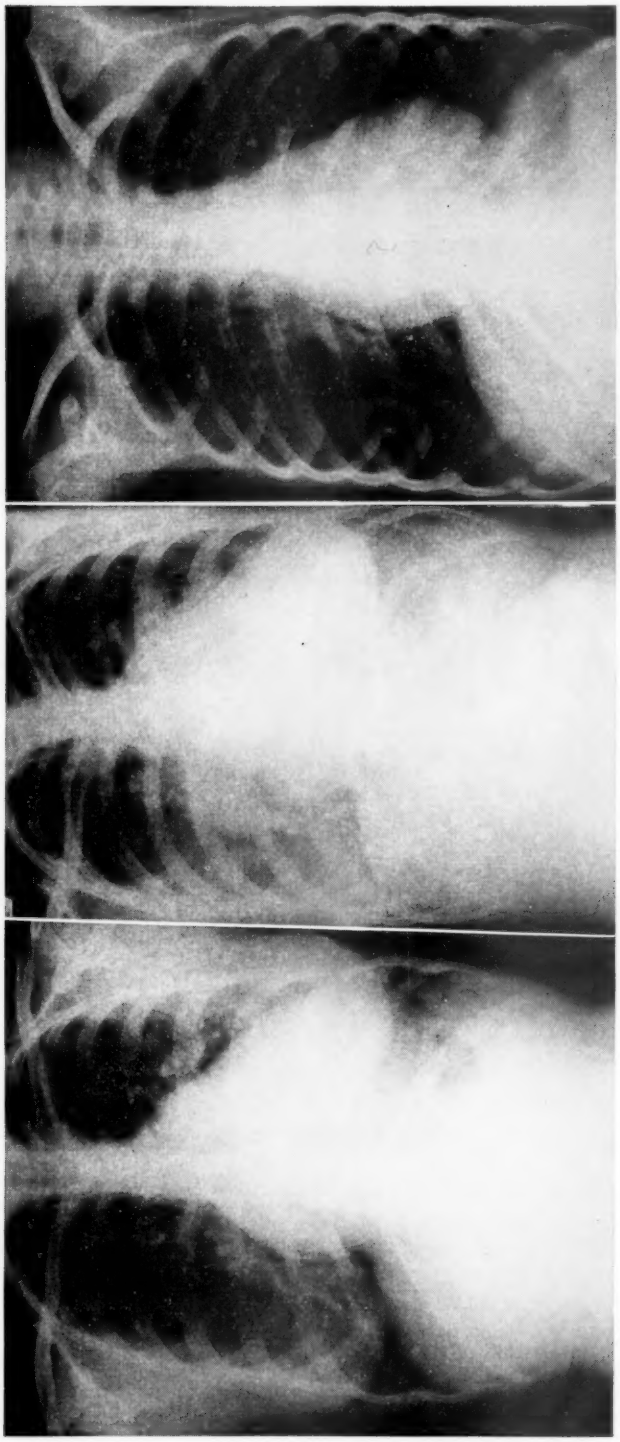
Fig. 3.—Pre- and postoperative (24 hours) chest x-rays of Case 3.

CASE 4.—A white woman, age 29 years, had been followed at Research and Educational Hospital Clinics for several years. At the age of 26, following the delivery of a child, she had noted exertional dyspnea and chest pain. Rigid cardiac management had improved her condition. Catheterization was carried out which confirmed the clinical impression of interatrial septal defect. The mean pulmonary artery pressure was 52 mm. Hg and the right ventricular pressure was 8.9/6 mm. Hg.

An attempt was made to close the defect utilizing hypothermia and inflow occlusion through a right thoracotomy. The defect was judged too large to close by this method. Five weeks later through a midsternal vertical incision utilizing extracorporeal circulation the defect was closed with ease. The postoperative course has been entirely uneventful. Chest x-rays show minimum reaction (Fig. 4).

DISCUSSION

Among the benefits derived from the midline incision was a marked shortening of the time of obtaining the exposure. The closure time is also shortened.



C.

B.

A.

Fig. 4.—Pre- and postoperative (24 hours and 12 days) chest x-rays of Case 4.

During the perfusion period the anesthetist was asked to continue manual respirations in order to further reduce pulmonary trauma by preventing appearance of areas of atelectasis due to collapse of portions of the lung.

The major benefit to accrue from this approach, however, is the avoidance of essentially all trauma to the lung and the freedom from postoperative splinting of the chest due to pain. Lack of lung damage during surgery may be the deciding factor in the cyanotic group whose vascular channels are undeveloped and the pulmonary hypertension group in which the vascular channels in the lung are pathologic. The ease of access to the right ventricle is at least equal to that obtained by the transverse incision; access to the cavae is safe and not difficult. The need for a graft entrance into the aorta may be an advantage because of the more physiologic nature of the arterial flow obtained.

We believe that a patent ductus could be divided through this incision without opening the adjacent mediastinal pleura although safety would be on the side of widening the exposure through the left pleural cavity. A persistent left superior vena cava could be temporarily occluded easily but cannulated only with difficulty if it were demonstrated to be the major venous drainage of the head and arms.

SUMMARY AND CONCLUSIONS

1. An application of the longitudinal sternal-splitting incision to cases operated upon under total body perfusion has been derived from experience with the incision in other intracardiac procedures.

2. The experience necessary for this more advanced application was gained with 31 operations for aortic and pulmonary stenosis under direct vision obtained by inflow occlusion and hypothermia.

3. The technique of cannulating the cavae by the standard method through this anterior approach is described. The arterial return to the patient has been established in 4 cases through a homologous artery graft implanted to the side of the ascending aorta.

4. Four patients are reported illustrating the advantage of this approach in avoiding trauma and collapse of either lung in patients with cyanotic heart disease and in patients with pulmonary hypertension of the acquired high flow type.

5. Trial of this approach encourages its routine use.

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Reappraisal

CONDUCTED BY CLARENCE DENNIS, M.D. ASSISTED BY ALFRED HURWITZ, M.D.

AUTOGENOUS VEIN GRAFTS

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IN 1953, our laboratory reported a series of experiments relating to the use of autogenous venous grafts as tissue for arterial replacement.[5] The primary complications which became apparent from these studies of autogenous venous grafts implanted into the abdominal aortas of growing pigs were the following:

(1) early thrombosis of the grafts—this was directly proportional to the degree of disproportion between the diameter of the graft and the recipient aorta—and (2) aneurysmal dilatation—this was present in a large percentage of the venous grafts which did not thrombose. These results, plus concomitant experiments which demonstrated a marked tendency for arterial homografts to undergo severe degenerative change when implanted into the thoracic aorta of growing pigs,[3] gave us incentive to further investigate means by which autogenous venous grafts might be utilized with greater efficacy.

A technique was devised whereby the frequent disproportion between the size of the vein (vein usually larger) and the recipient artery at the time of implantation might be corrected. This technique was named plication.[6, 7] The vein wall was merely infolded (plicated) by means of interrupted Lembert-type sutures of 6-0 silk placed 2 mm. apart. Using this method, the incidence of early thrombosis due to turbulent flow in the disproportionate grafts was markedly reduced (Table I). This complete lack of early thrombosis is in contrast to the 78 per cent incidence which occurred without plication in autogenous venous grafts implanted into the abdominal aorta of dogs when the grafts were 20 per cent larger in diameter than the recipient aorta.

TABLE I. RESULTS OF PLICATION VENOUS AUTOGRAFTS

	NUMBER	EARLY COMPLICATIONS (THROMBOSIS)	LATE COMPLICATIONS	
			THROMBOSIS	DILATATION
Abdominal Aorta (Dog)	10	0	1	1*
Thoracic Aorta (Pig)	6	0	0	6

*Only this animal examined for dimensional change.

The problem of late venous graft dilatation has not been so easily solved. It was observed that under the extreme stress of graft implantation into the

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thoracic aorta of growing pigs, 3 of 10 grafts failed to undergo the expected dilatation.[2] When these experiments were reviewed, it was found that the venous graft at the time of implantation was smaller in its diameter than the host thoracic aorta. It was hoped that this observation of graft biterminal negative disproportion at the time of implantation might markedly decrease the incidence of late graft dilatation if all grafts implanted were similarly reduced in diameter to a degree sufficient to produce biterminal negative disproportion as related to the host aorta. The result was disappointing.[7] Six venous grafts implanted into the thoracic aorta of growing pigs were reduced to a size 29 per cent smaller in diameter than the recipient aorta. Dilatation did occur in every instance; however, the dilatation was less severe than any previous similar experiment performed without plication.

A. *B.*

Fig. 1, *A*.—Arteriogram of left femoral artery in a 58-year-old white man. A block is present at the entrance of this artery into the adductor canal. *B*, Femoral arteriogram of left leg 1¼ years after insertion of an autogenous saphenous vein graft into blocked segment depicted in *A*. Note lack of dilatation of the vein graft.

Another series of experiments was performed utilizing a live muscle support in an endeavor to prevent late dilatation of venous autografts.[4] A viable intercostal muscle bundle was used to support fresh venous autografts implanted into the thoracic aorta of growing pigs. The muscle surrounding these venous grafts did not buttress them sufficiently to prevent a high incidence of graft dilatation. In this small number of experiments, the muscle support did decrease the incidence of early graft rupture to nil, a complication which we had seen previously in 20 per cent of unsupported venous grafts implanted into the thoracic aorta of growing pigs.

Further attempts were made to prevent venous graft dilatation. Hevea latex, a known tissue irritant, which produces a fibroblastic response, was applied to venous grafts implanted into the thoracic aorta of 7 weanling pigs.[7]

Although the walls of these grafts were thick and fibrotic, areas of dilatation occurred in all the grafts. The aneurysms which developed were diffuse with superimposed "daughter" aneurysms. Another fibroblastic agent, dicetyl phosphate, has been similarly studied.[1, 8] Forty per cent of the grafts treated with this substance were isodimensional at the time of graft harvest, 8 months after implantation. Although the application of dicetyl phosphate seemed to exert a restricting effect on the subsequent enlargement of these fresh venous autografts implanted into the thoracic aorta of growing pigs, the following factors noted during these experiments seem to militate against its general usage for such a purpose: (a) failure to provide prompt control of a tendency toward dilatation, (b) a higher incidence of atheromatous or calcific degeneration in the grafts, and (c) late cicatricial stenosis of the graft.

From the foregoing, it is readily apparent that an adequate answer for prevention of venous graft dilatation when such grafts are placed in defects in the aorta, has yet to be found. Vein plication has been proved to be an effective method for preventing artery-vein disproportion at the time of implantation with resultant decrease in turbulent blood flow and concomitant early thrombosis. We have been very pleased to date with the use of saphenous vein autogenous material for arterial replacement below the bifurcation of the femoral artery at the groin. The muscle support present at this level seems to preclude significant dilatation (Fig. 1). The saphenous vein is of such a size to rarely necessitate the use of plication. Replacement materials for lower extremity arterial defects at the present time in our institution include the following in order of choice: (1) autogenous saphenous vein, (2) plastic prosthesis (Teflon), and (3) freeze-dried arterial homograft.

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THE PREVENTION OF ILEOSTOMY DYSFUNCTION

A Modification of Technique

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IN THE October, 1956, issue of Surgery, we published a paper on the general problem of ileostomy dysfunction and described a plan of operative management in the fashioning of an ileostomy designed to eliminate this serious complication. The thesis was advanced that the basic cause of dysfunction is the development of a serositis of the exteriorized segment of ileum which extends deeper into the abdominal cavity setting up an inflammatory reaction of the peritoneum covering the terminal foot or 2 of ileum and resulting in haphazard adhesions, thus causing partial intestinal obstruction. We are convinced that the outpouring of large quantities of thin fluid with electrolyte loss, the so-called ileostomy dysfunction, is the pathognomonic sign of partial obstruction of the small bowel and that the most common cause is a localized peritonitis involving the terminal foot or two of ileum.

The operative program advocated in the paper referred to included: (1) removal of a button of skin and subcutaneous fat at the selected site of the ileostomy, (2) fixation of the mesentery of the terminal ileum to the parietal peritoneum to prevent prolapse, (3) a modified Noble plication of the terminal 2 feet of ileum to fix the bowel in a position of the surgeon's choice, thereby minimizing haphazard adhesions, (4) eversion of the full thickness of ileum of the exteriorized end, the Brooke maneuver, to minimize serositis and hasten maturation of the ileostomy, and (5) the immediate application of a plastic bag to eliminate skin excoriation from the ileal discharges.

With the exception of the one patient mentioned in the original paper who developed a high obstruction which caused his death, the almost complete elimination of all ileostomy complications in a consecutive series of 34 patients was unique in our experience. We dared to believe that the serious and often fatal complication of ileostomy dysfunction had been eliminated. There then occurred 2 unpleasant experiences in Patients 35 and 36. Both developed dysfunction a few days after operation, one of considerable severity which continued for 3 weeks. With continuous accurate intravenous replacement of large quantities of fluid and electrolytes, spontaneous recovery took place. During the 3-week period, it was easy to palpate a rather firm matted mass immediately subjacent to the ileostomy. During the fourth week, the mass rapidly became smaller and finally disappeared. There was little fever and the leukocyte count varied with the state of hydration. The second patient also developed dysfunction during the first postoperative week and, in spite of heroic measures, died suddenly on the seventeenth day. The post-mortem examination disclosed a low-grade diffuse peritonitis without demonstrable cause. There was no adhesive band and no obvious perforation, but the major peritoneal reaction was centered in the neighborhood of the plication procedure.

From the train of events in the postoperative course of these 2 patients, we believe it is reasonable to assume that the very maneuver of plication, designed to eliminate dysfunction, produced it. It is reasoned that in sewing together the 4 loops of terminal ileum minute perforations were produced, in spite of the use of very fine needles and suture material, resulting in a localized inflammatory process, possibly with minute abscesses, with subsequent partial obstruction and dysfunction. Fortunately, in one patient, spontaneous resolution took place and a full recovery ensued. The second patient succumbed in spite of massive antibiotic therapy and adequate fluid and electrolyte replacement.

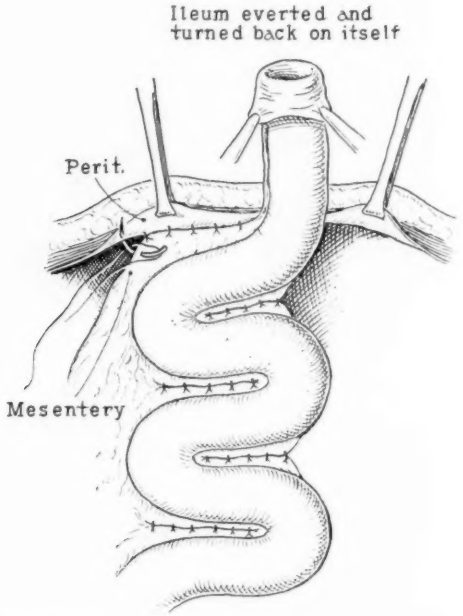

Fig. 1.—Details of the plication of the terminal 2 feet of ileum in which the mesentery of each opposing 2 loops of ileum are sutured with interrupted stitches. The sutures are placed approximately one-half inch below the mesenteric attachment of the bowel; care is taken to avoid puncturing the vessels in the mesentery.

As a result of this experience, we have changed the technique of the plication procedure in order to obviate the hazard of needle puncture of the bowel wall. We now approximate the 2 loops of ileum to be plicated and place interrupted 4-0 silk sutures in the mesentery about 3/8 of an inch below the bowel itself. Six to ten sutures should suffice to approximate each 2 loops of ileum. The accompanying illustration indicates clearly the details of this maneuver. By avoiding the placing of sutures in the usually thin wall of ileum, we believe we will eliminate another cause, albeit inadvertent, of ileostomy dysfunction.

Case Reports

EXTRINSIC ESOPHAGEAL OBSTRUCTION AND POSTOPERATIVE CHYLOTHORAX

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SEVERE dysphagia presenting as the initial and only symptom of extra-esophageal pathology appears to be a very unusual occurrence.

Chylothorax following mediastinal surgery is apparently rare enough to warrant publication of nearly every case observed.[4, 5]

The occurrence of both conditions in the same patient seems, thus, well worth recording.

REPORT OF CASE

N. H., a 41-year-old married man, was referred to the Department of Thoracic Surgery on Oct. 22, 1953, because of dysphagia which had appeared 5 months before admission. At first he noted difficulty in swallowing solid food only; however, later on, even fluids were swallowed only with great effort. He had lost 5 Kg. weight during the previous 4 months.

Physical examination failed to reveal pathologic findings and his general condition was satisfactory. Blood counts, blood chemistry, urine analysis, and so forth showed normal values. The routine chest roentgenogram was reported as within normal limits.

Esophagoscopy revealed a considerable narrowing of the esophageal lumen about 8 cm. distal to the cricopharyngeus which prevented passage of the scope, permitting introduction of a very thin sound after debris of food had been cleared by aspiration. The mucosa appeared normal at the site of the narrowing, apart from inflammatory changes; there was no ulceration.

X-ray examination of the esophagus by barium swallow revealed considerable narrowing of the entire middle third of the esophagus (Fig. 1). Thin barium passed very slowly whereas the barium pill remained in the dilated segment proximal to the obstruction. The mucosa appeared intact.

Esophagoscopy and x-ray findings gave the impression that the obstruction in the middle third of the esophagus was due to compression from without.

Repeated x-ray studies of the lungs, the heart, and great vessels, including frontal, lateral, and oblique tomographies of the entire chest and mediastinum did not contribute further information with regard to the pathology present.

Exploratory thoracotomy was therefore decided upon.

On Nov. 4, 1953, the right chest was opened through the bed of the fourth rib. The lung was adherent to the chest wall by dense adhesions and, in order to free it, extrapleural dissection was necessary. The lung itself was free of gross pathology. The thoracic esophagus proximal to the level of the azygos vein was found to be dilated. The middle third of the esophagus was surrounded by a firm mass adherent to all neighboring structures, including the aortic arch, the bifurcation of the trachea, and the hilum of the right lung from the level of the azygos vein to the area of the inferior pulmonary vein extending

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into the upper part of the interlobar fissure. A piece of tissue was removed for frozen section biopsy and diagnosed as malignancy, probably metastatic adenocarcinoma. Complete removal of the mediastinal mass which densely adhered to vital vascular structures was obviously impossible. The mass could be dissected, however, from the esophageal wall which was not invaded, and the middle third of the esophagus could be shelled out,

Fig. 1.—Preoperative esophagogram showing considerable narrowing of the middle third of the esophagus.

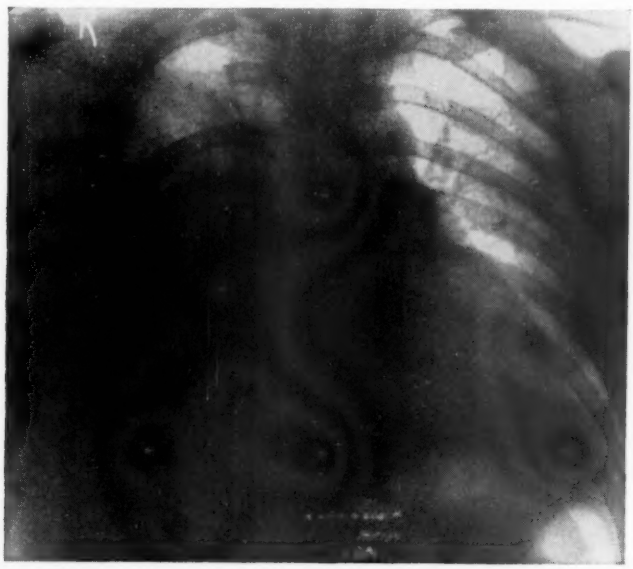

Fig. 2.—Seventh postoperative day chest roentgenogram showing opacity of right hemithorax.

thereby relieving the compression. Thereafter a large Levine tube could be easily passed into the stomach. The chest was closed leaving a drainage tube in the eighth intercostal space connected to a water-seal system.

The early postoperative course was smooth. There was good re-expansion of the lung and primary healing of the thoracotomy. The patient began to eat normally from the third day after operation and had no difficulty in swallowing even solid food. On the seventh postoperative day he complained of pressure in the right chest and dyspnea. The roentgenogram (Fig. 2) showed opacity of the lower two-thirds of the right hemithorax. By thoracentesis 600 c.c. of a thin milky fluid was aspirated. Microscopic examination of this fluid showed the presence of fat globules confirming the clinical diagnosis of chylothorax.

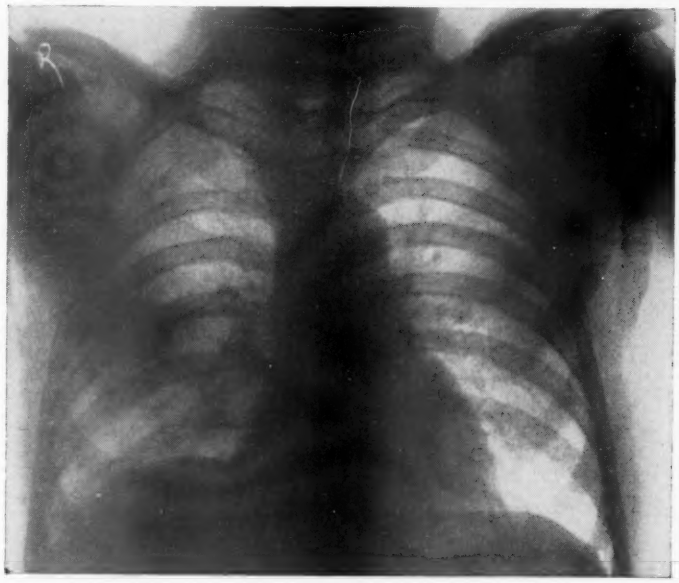

Fig. 3.—Chest roentgenogram four weeks after operation showing clearing of chylothorax.

After the aspiration the patient felt considerable relief of pressure and dyspnea which lasted for only 2 days until the chylothorax had refilled. Between the ninth and the twenty-fourth postoperative day, 8 additional thoracenteses had to be performed removing quantities of chyle varying from 400 c.c. to 1,600 c.c. All in all, 8,600 c.c. were evacuated. During the same period the patient was kept on a high caloric, low fat, high protein and vitamin diet, supported by intravenous Amigen infusion and antibiotics. Blood proteins and electrolytes were maintained at normal levels and his general condition remained satisfactory. On the twenty-fifth postoperative day, after evacuating the chylothorax, 20 c.c. of 35 per cent Diodone were introduced in an attempt to visualize the location of the thoracic duct fistula. This was unsuccessful as the contrast medium did not show clearly enough.

Under the assumption that the chylous fistula in this patient was produced by traumatization of the thoracic duct in an area of malignant tissue, extending throughout the mediastinum, rethoracotomy with the view of ligating the duct was not considered. A trial with x-ray therapy was therefore undertaken and the patient received, during the following 10 days, 8 applications of 1,500 r. During that period only 2 thoracenteses were necessary and the amount of chyle aspirated was much smaller. The patient felt comfortable and had no complaint whatsoever. Chest roentgenogram (Fig. 3) revealed complete clearing of the right hemithorax. A control esophagogram (Fig. 4) taken at the same time showed normal filling of the entire esophagus with undisturbed passage of even heavy barium.

The patient was discharged on Dec. 14, 1953, in good general condition and was able to eat normally.

He was re-examined at 3-month intervals and was free of complaints with the exception of some pain in the thoracotomy scar. One year after the operation he had gained 10 Kg. in weight, looked and felt completely healthy, and was able to do heavy physical work. Chest roentgenograms and esophagograms repeatedly taken continued to show normal findings. At the last examination, in December, 1955, 2 years after operation, his condition was found to be excellent.

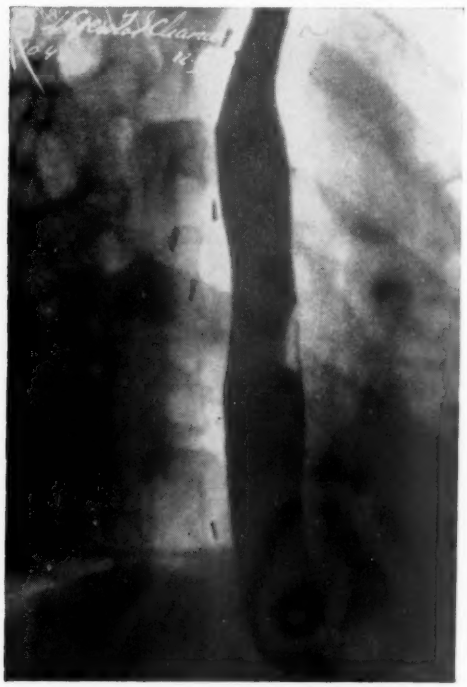

Fig. 4.—Esophagogram four weeks after operation showing normal filling of entire esophagus.

This unexpectedly favorable clinical course hardly fit in with the diagnosis of metastatic malignancy. The surgical specimen from the mediastinum was, therefore, re-examined by the pathologist who withdrew his former diagnosis and described the lesion as a nonspecific inflammatory process with marked fibrosis.

Case Summary.—Extrinsic obstruction of the middle third of the esophagus in a 41-year-old man causing severe dysphagia has been described. The preoperative diagnosis was mediastinal malignancy and, at thoracotomy, frozen sections of the mediastinal mass compressing the esophagus apparently confirmed this diagnosis. Chylothorax appeared following operation and was effectively treated conservatively. Dysphagia was completely relieved and the patient made a surprising recovery, being in excellent condition 2 years after operation. Re-examination of the surgical specimen at that time revealed a nonspecific inflammatory process.

COMMENT

Three aspects of this case deserve comment: (1) the severe dysphagia caused by pressure from a mediastinal mass; (2) the postoperative chylothorax responding to conservative treatment; and (3) the error in the pathologic evaluation of the surgical specimen.

Only a few instances of severe dysphagia as the initial and only symptom of nonspecific inflammatory mediastinal disease are described in the literature. In nearly all of them the presumptive clinical diagnosis was tumor. Samson, Heaton, and Dugan[6] report on a 27-year-old woman in whom a preoperative diagnosis of dermoid compressing the esophagus was made. At operation the mass proved to be "tuberculoma" containing caseous material. Goldman,[3] in discussing the above report, describes a case of his own where a preoperative diagnosis of carcinoma of the esophagus had been made. At thoracotomy he found a chronic inflammatory mediastinal mass which had perforated into the esophageal wall. The final diagnosis was nonspecific mediastinal granuloma. Samson and Dugan[7] report on a 29-year-old woman in whom dysphagia was presumed to be due to a hiatus hernia. At operation a tuberculous abscess anterior to the esophagus was found and removed. The same authors quote a case observed by Clerf (1940) in which the esophagus was narrowed at the level of the aortic arch by a tuberculous abscess posterior to it. This abscess drained into the esophageal lumen resulting in relief of dysphagia.

Garamella and co-workers[2] report on 3 cases of subcarinal mediastinal granulomas. In 2 of them dysphagia was an important symptom. The preoperative diagnosis in both of them was esophageal tumor. In the other case, the presence of a mediastinal granuloma was suspected preoperatively. In this case the pathologic diagnosis was granulomatous inflammation of the mediastinal lymph nodes, probably tuberculosis. In the 2 other cases chronic granulomatous inflammation of mediastinal lymph nodes was the pathologic diagnosis. However these authors point out that tuberculosis must be assumed to be the underlying condition even in these cases.

Including their own cases, they collected from the literature 39 cases in which subcarinal mediastinal granulomas, probably of tuberculous origin, were surgically removed. In the majority of these, cough, dyspnea, and chest pain were the predominant symptoms.

In only 6 cases was severe dysphagia the predominant clinical symptom. Our case should apparently be added to this group. The final histologic diagnosis in our patient was nonspecific inflammation with extensive fibrosis which does not disprove tuberculous etiology.

The appearance of chylothorax in our patient on the seventh postoperative day was certainly due to trauma to the thoracic duct during the surgical dissection in the mediastinum when the esophagus was freed. Since the report of Lampson,[5] traumatic chylothorax following surgical intervention in the chest is a well-known complication, and it seems peculiar indeed that, notwithstanding the large number of major intrathoracic operations carried out everywhere, only 13 cases of postoperative traumatic chylothorax have been collected from the literature between 1948 and 1954.[4] Lampson directed attention to the seriousness of this complication and reported a mortality of 40 per cent for his entire series of 18 cases which comprised also nonsurgical chest and neck injuries.

Several authors (Peet and Campbell, 1943; Lampson, 1948; Goorwitch, 1955, and Brewer, 1955) have, therefore, advocated surgical ligation of the injured thoracic duct within the chest and have thus succeeded in considerably reducing the high mortality of this condition. In our patient, rethoracotomy with the view of ligating the duct was rejected since his condition was considered to be metastatic mediastinal malignancy.

Conservative treatment consisting of repeated thoracentesis with intravenous supportive therapy was therefore the only choice. The attempt to visualize the fistulous tract by injection of Diodone was unsuccessful; however the irritative properties of this hypertonic solution may have had some effect as in the case of Touroff and Seley[9] who, by injecting Lipiodol, successfully achieved closure of a chylous fistula in the mediastinum. It is equally uncertain which role, if any, the x-ray treatment played in the closure of the fistula in our patient. X-ray therapy was advocated for the treatment of chylothorax by Van Nuys in 1931.[8]

It seems probable that the chylous fistula in our patient would have closed spontaneously even without application of x-rays. Similar cases in which conservative treatment by thoracentesis brought about recovery are on record (Goorwitch[4]). However, the mortality reported in the conservatively treated group was 19 per cent whereas all patients in whom the duct was ligated recovered.

Another noteworthy point in this case is the erroneous pathologic diagnosis which was rectified 2 years later only when the clinical course proved to be inconsistent with the presence of metastatic malignancy in the mediastinum. This shows that the pathologist as well as the surgeon may be wrong in evaluating uncommon pathology in the operating room. The patient's family was given full information on the findings at the operation and the prognosis was accordingly described as extremely bad. The erroneous pathologic report confirmed the presumptive clinical diagnosis of mediastinal malignancy, and it is freely admitted that no other differential diagnosis was entertained at that time. The patient's physicians who attended him before his hospital admission were so certain of this diagnosis that they did not even consider surgical exploration but sent the patient to x-ray therapy.

This patient's history as well as similar ones quoted from the literature,[2, 3, 6, 7] shows that severe extrinsic obstruction of the esophagus may occasionally be caused by an inflammatory process in the mediastinum (tuberculous or nonspecific) which can be successfully treated by surgery.

SUMMARY

The clinical entity of extrinsic esophageal obstruction due to an inflammatory process in the mediastinum is reported, based on our own observations and cases collected from the literature. The pathogenesis, differential diagnosis, and surgical treatment of this condition is discussed.

The complication of traumatic postoperative chylothorax and its management is described.

The pathologist as well as the surgeon may be wrong in evaluating uncommon conditions during exploratory surgery.

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SIMULATED MITRAL STENOSIS BY METASTATIC MELANOMA

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MUCH interest has been aroused in the past decade in the ante-mortem diagnosis of both primary and secondary tumors of the heart. The diagnosis of primary tumors is important for possible permanent eradication through surgery[2, 4, 8] as over 70 per cent are benign.[11] Secondary tumors are diagnostically important, since the relief of the various cardiac symptoms they produce may sometimes be accomplished through present and future methods with external irradiation, carcinolytic compounds, and radioactive materials. Surgical attack is generally contraindicated in secondary cardiac lesions.

Until recently the frequency of metastatic lesions to the heart was not generally appreciated. The first ante-mortem diagnosis of a secondary cardiac tumor was reported by Rösler,[13] in 1924. Twenty-one per cent of 500 consecutive deaths due to neoplastic disease at the Memorial Center in New York, in 1953, had cardiac metastases.[3] In the Memorial series cardiac metastasis was present at autopsy in 44 per cent of the patients with leukemia, 24 per cent of those with lymphoma, and 12 per cent of those dying of visceral and cutaneous tumors. Cardiac invasion by visceral and cutaneous tumors was most frequent in malignant melanoma (60 per cent), carcinoma of the breast (33 per cent), and carcinoma of the lung (31 per cent).

In large series of consecutive autopsies the over-all incidence of cardiac metastases varies from 5.3 to 1.7 per cent and in those dying of malignant disease from 21 to 2.5 per cent.[3, 6, 11, 14] Significantly, the more recent the report the higher the percentages of metastasis.

All authors agree that the heart and pericardium are subject to metastasis from almost all malignant tumors. When the heart is involved, generally the tumor is in multiple other organs, as solitary secondary tumors of the heart are rare.

A patient with a clinical diagnosis of mitral stenosis was subjected to thoracotomy for corrective mitral valve surgery. Cardiac metastasis from a primary malignant melanoma of the eye enucleated 13 years previously was diagnosed at surgery. A detailed case report appears warranted because of the infrequency of secondary metastasis simulating mitral stenosis.

CASE REPORT

B. A., a 43-year-old white woman had been in good health until December, 1953, at which time she developed palpitations, tachycardia, 2-pillow orthopnea, and mild exertional dyspnea. In February, 1954, the patient had 2 episodes of syncope. During this interval her cardiac symptoms were intermittent.

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In May, 1954, she was admitted to the Ohio State University Health Center for cardiac evaluation. During the preceding months she had lost 13 pounds but had no marked increase in her symptoms. She never had peripheral edema, cough, hemoptysis, or chest pain. The past history was positive for scarlet fever but negative for rheumatic fever. In December, 1942, the patient had enucleation of the left eye for melanotic sarcoma of the choroid.

Positive physical findings included slightly diminished breath sounds throughout the lungs, with a few fine râles. The heart was enlarged to the anterior axillary line with a heaving pericardial thrust especially at the apex. No thrills were present. The rate was 84 with an irregular rhythm. At the apex was a loud, harsh murmur that seemed to be diastolic, with a loud snapping M_1 followed by a soft, sometimes absent, M_2. No systolic murmur was heard at the apex. At the left sternal border was heard a Grade 1 or 2 systolic murmur and a questionable soft diastolic murmur. At the second right intercostal space both A_1 and A_2 were audible, with a soft systolic murmur present without radiation into the neck. At the second left intercostal space and further to the left there was a loud second heart sound (P_2). A systolic murmur was present in this latter area and again a questionable diastolic murmur. The liver was palpated 3 fingerbreadths below the right costal margin and extended across the midline. It was smooth, rounded, and nontender, without palpable nodules. The spleen was 2 fingerbreadths below the left costal margin, was firm, and moved with respiration.

Roentgenographic studies of the heart and chest showed the transverse cardiac diameter to be enlarged 50 per cent for the patient's height and weight (Fig. 1). The enlargement was primarily in the left atrium (Fig. 2) and ventricle, but also some evidence of right heart enlargement was present. The cardiac pulsations were of deep amplitude in both ventricles, poorly sustained in the aorta. The barium filled esophagus was displaced toward the left and posteriorly by a markedly enlarged left atrium. No calcification in the cardiac shadow was seen. The vascular markings were prominent. The roentgenographic diagnosis was cardiac hypertrophy and dilatation due to rheumatic heart disease with mitral stenosis and insufficiency, with probable aortic insufficiency.

The electrocardiograms showed a first degree heart block with sinus arrhythmia, thought possibly due to digitalis intoxication. The P-R interval was 0.52 second, occasionally 0.56 second. The P waves were consistent with mitral stenosis.

Cardiac catheterization studies showed the blood pressure in the left brachial artery to be 105/73 mm. Hg; the right atrium, 25/2 mm. Hg; and the right atrium breath holding, 11/3 mm. Hg. The pulse contour of the right atrium was consistent with some degree of tricuspid stenosis. The right ventricle and pulmonary artery could not be entered due to marked irritability of the ventricle. The arterial saturation was normal at rest with a normal exercise tolerance indicating a good alveocapillary filling. The diagnosis of mitral stenosis was sustained by the cardiologists and, on their advice, in view of the long P-R interval, the patient was discharged without digitalis.

The patient returned 2 weeks later for surgical correction of the mitral stenosis. A repeat electrocardiogram showed no change in the P-R interval. On June 16, 1954, a left submammary thoracotomy was performed. The pericardial sac was tense due to a marked increase in the intrapericardial fluid. Five hundred cubic centimeters of a serous, slightly brownish, turbid fluid escaped on opening the pericardial sac. The left atrial appendage and atrium were markedly enlarged. Exploration of the posterior region of the heart revealed multiple black tumors of the left ventricle which were extremely hard and had the appearance of melanosarcoma. The diagnosis was proved on biopsy.

Six months later the patient was admitted to another hospital in a terminal condition. Similar but more severe cardiorespiratory signs and symptoms were present as on previous admissions. An electrocardiogram showed a heart block with a 2 to 1 atrioventricular response and changes which were thought to be consistent with pericardial effusion. The patient died in several days of acute congestive heart failure.

Fig. 1.

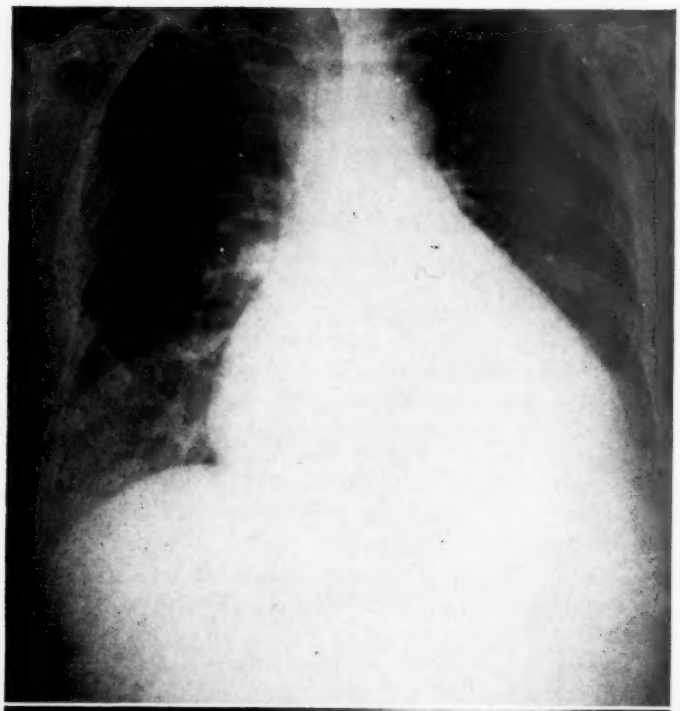

Fig. 2.

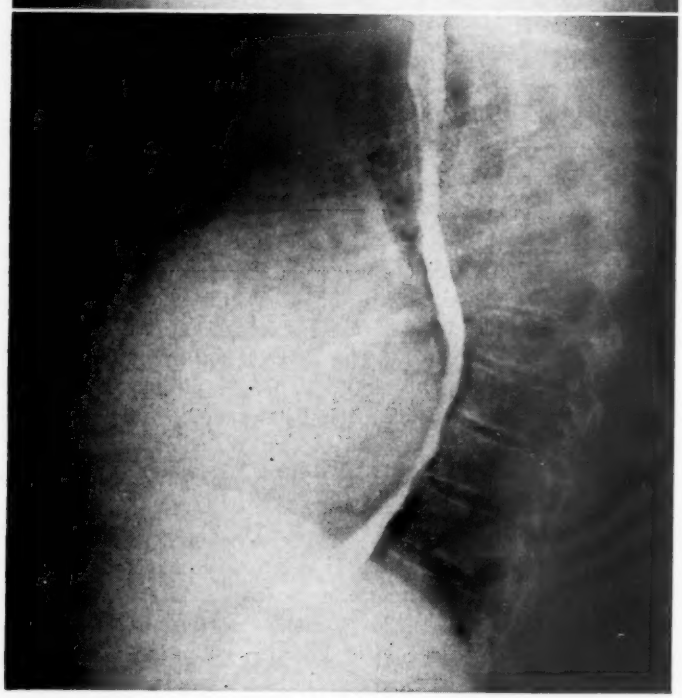

Fig. 1.—Posteroanterior roentgenogram of the chest showing cardiac enlargement.

Fig. 2.—Left lateral roentgenogram of the chest demonstrating left atrial and right ventricular enlargement.

Fig. 3.

Fig. 4.

Fig. 3.—Heart opened through the left atrium and left ventricle showing almost complete replacement of the left atrial walls and interatrial septum by metastatic melanoma. The overgrowth of tumor is noted to impinge on the mitral valve area although the valve itself is essentially normal. Metastatic tumor is seen variously dispersed throughout all the cardiac musculature.

Fig. 4.—Left ventricle showing the mitral valve and lower margin of atrial wall.

The autopsy revealed the heart to be markedly enlarged. There was a large deposit of metastatic tumor involving primarily the posterior surface of the heart and the left atrium (Fig. 3). The neoplasm markedly infiltrated the walls of the left atrium and extended into the interatrial septum. The involved atrial walls were markedly thickened, measuring 4.5 cm., thus producing a corresponding reduction in the volume of the left atrial chamber. Smaller deposits of tumor were present throughout other areas of the heart. The valves (Fig. 4) showed no significant abnormality. Metastatic tumor occluded the distal end of the left circumflex coronary artery and the descending branch of the right coronary artery 3 cm. from its origin. The combined weight of the heart and tumor was 740 Gm. In addition to the massive deposits of tumor in the heart there were also scattered small infiltrations in the mediastinum, lungs, intestines, pancreas, ovaries, adrenal glands, and various lymph nodes; no tumor was present in the liver.

DISCUSSION

Frequently a patient will live for as long as 13 years following removal of a primary malignant melanoma of the choroid. Fifty to fifty-five per cent of patients survive for 5 years and 38 per cent for 10 years.

While metastatic melanoma is the subject of this case report, other tumors frequently metastasize to the heart.[3, 6, 11, 14] The ante-mortem diagnosis of cardiac metastasis is difficult. The inconsistency and unreliability of the cardiac signs and symptoms[1, 3, 4, 14] together with the low index of suspicion secondary to the supposed rarity of the lesion accounts for the infrequency of the diagnosis. In a review of the hospital charts of the 500 consecutive patients dying of malignant disease described by Bisel, Wroblewski, and LaDue,[3] only 8.8 per cent had ante-mortem symptoms of such significant magnitude that cardiac metastasis could have been suspected; however, electrocardiographic changes of significance were present in 29 per cent of these cases. These authors, as well as others,[9, 10, 12, 16] found little correlation between the size and extent of the cardiac metastasis and the clinical manifestations of heart disease.

In the case presented, the extremely long P-R interval of 0.52 second could not be explained preoperatively and was the major discrepancy in the diagnosis of simple valvular mitral stenosis. This would support the much higher incidence and emphasize the significance of electrocardiographic versus clinical symptoms in metastatic cardiac disease. It is easy to postulate that tumor tissue variously dispersed throughout the heart would produce abnormal and bizarre tracing and rhythms considerably sooner and more notable than clinical symptoms.

A high index of suspicion of cardiac metastasis should be entertained in patients with a history of previous malignancy and showing various abnormal cardiac rhythms, bundle branch or auricular-ventricular blocks, or Adams-Stokes syndrome when no explanation such as evidence of previous rheumatic disease, arteriosclerotic heart disease, toxic state, or history of coronary infarct is present.[1, 4, 7]

CONCLUSIONS

1. The frequency of cardiac metastasis in patients with neoplastic disease is relatively high.

2. Primary and secondary tumors of the heart frequently produce enough findings to place this diagnosis high on the list of suspected cardiac lesions, especially when corrective surgery is advocated.

3. Cardiac metastasis should be suspected in patients with previous neoplastic disease if cardiac problems develop in the absence of other obvious cardiac disease.

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TRAUMATIC CHYLOTHORAX

Case Report and General Discussion

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In 1948 Lampson[16] reported the first successful transthoracic ligation of the thoracic duct in a case of traumatic chylothorax. Since the publication of his success, 32 cases of traumatic chylothorax have been reported. Of these, 16 were treated successfully by ligation of the duct either in the chest or neck.[1, 2, 6, 9, 14, 20-22, 24, 26, 27, 32] One additional case was treated by anastomosis of the thoracic duct to the azygos vein with a successful conclusion.[11] Fourteen cases were treated by conservative methods with 2 deaths.[3-5, 7, 8, 10, 12, 18, 19, 21, 25, 28, 29] And the final case of the 32 was reported as an unsuspected bilateral traumatic chylothorax discovered at autopsy in an individual with other serious injuries.[33]

It is only fitting to record, in contrast to the present results in the therapy of this injury, that until Lampson's case was reported the over-all mortality in the treatment of traumatic chylothorax was 50 per cent and that surgical intervention had met with complete failure. Up to 1948 a remarkable variety of conservative measures were employed therapeutically. All were directed toward correcting the mechanical effects of the chylothorax, toward the maintenance of nutrition, and toward the promotion of healing. Many of these measures remain valid; however, the trend has been toward early surgical intervention. This trend has been based on the success of recent surgical efforts and on the difficulties encountered in maintaining the nutrition and hydration of these patients when spontaneous closure of the fistula fails to occur early. Surgical intervention is indicated when it becomes apparent, as it often does in ten to twelve days, that supportive, conservative therapy has failed to close the injured duct and failed to support the patient.

Traumatic chylothorax results from direct or indirect violence or surgical misadventure. Particularly has the surgical attack upon the thoracic sympathetic system, the esophagus, and the thoracic blood vessels led to this complication. Injuries of violence whether due to automobile accidents, gunshot wounds, or stab wounds remain a common cause of chylothorax. It should not be forgotten that chylothorax may follow minor trauma during which sudden hyperextension of the spine[3, 21] or a sudden change in intrathoracic pressure[18] will have occurred.

Traumatic chylothorax may result following injury to the thoracic duct, either when it is torn or severed within its thoracic course, when it is injured within the neck and a traumatic communication through the dome of the pleura is present, or when it is injured in the neck and the chyle descends in the

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visceral compartment and, under pressure, ruptures the mediastinal pleura.[8] In the case reported here chylothorax resulted from a stab wound in the neck which severed the cervical portion of the duct, the chyle passing through a tear in the dome of the pleura to fill the left thorax (Fig. 1).

CASE REPORT

C. C. (Macon Hospital No. 171235), a 34-year-old Negro man, was admitted to the Emergency Room on Oct. 21, 1953, with a stab wound of the left supraclavicular area. The patient was cold and clammy with a blood pressure of 70/50. A one inch-long stab wound was present just above the left clavicle over the area of the scalenus anticus. This was his only injury. The left chest was dull to percussion and breath sounds were decreased. A portable chest film demonstrated a massive accumulation of fluid in the left chest. 1,250 c.c. of blood and 75 c.c. of air were removed by aspiration. After this thoracentesis and the transfusion of 1,000 c.c. of whole blood, the patient's condition improved and became stable. The neck wound was sutured and the patient was transferred to the ward.

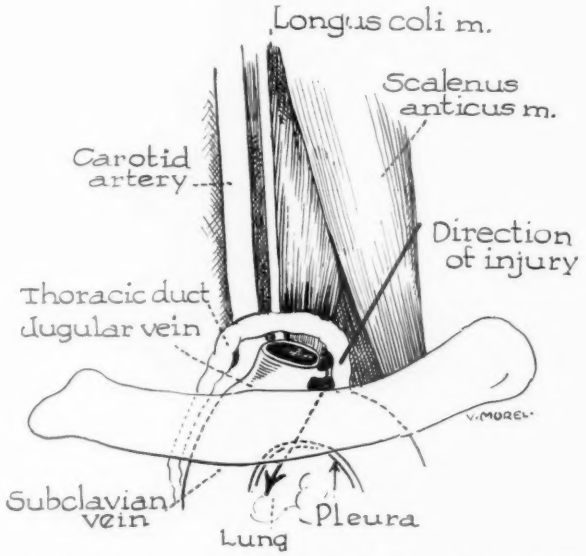

Fig. 1.—Sketch demonstrating concomitant injury to thoracic duct and pleura producing chylothorax.

On the following day 1,000 c.c. of blood were aspirated from the chest. On succeeding days, October 23 to October 29, six thoracenteses yielded 6,700 c.c. of fluid which early could best be described as sanguinopurulent but, by October 26 was "milky." Cultures of this material were consistently negative and showed a high concentration of fat with Sudan III.

The clinical impression at this time was that the thoracic duct had been severed in its cervical portion and was draining into the left pleural cavity. The neck wound had healed. The patient's condition by October 29 had become precarious. Weight loss, dehydration, weakness, hypotension, and cough were marked despite determined efforts to maintain his nutrition and hydration. The lung was only partially expanded, but there was no evidence of clotting of the chyle.

October 30, nine days after the injury, the patient was brought to surgery for exploration. On examination in the operating room moderate mediastinal shift was apparent. Under local anesthesia a rubber catheter was introduced into the left chest and connected to closed suction. Three thousand eight hundred cubic centimeters of chyle were gradually removed although 1,000 c.c. had been aspirated from the left chest the night before surgery. After two hours the patient's condition stabilized. Under endotracheal anesthesia a

transverse incision was made above the clavicle excising the skin wound. The stab wound had entered the lateral edge of the sternomastoid muscle, passed medial to the scalenus anticus cutting it slightly, and passed behind the subclavian vein to pierce the dome of the pleura, at which point a small tributary of the jugular vein had been severed as well as the thoracic duct. In order to expose this area the medial half of the clavicle was removed. While dissecting in this remarkably indurated area, hemorrhage occurred which could only be controlled by pressure. The chest was then opened through the third intercostal space anteriorly cutting the costochondral junctions of the third and fourth ribs. With the operator's hand within the thorax applying pressure under the area of the knife wound, suture ligation of the originally injured blood vessel, the source of the admission hemothorax, controlled the hemorrhage. Chyle was identified as coming from an indurated, inflamed cord of tissue which led to the subclavian vein. This was doubly transfixed. Despite the absence of any observable peel or fibrosis, the left lung under pressure would expand to only two-thirds of normal. A considerable portion of visceral pleura was removed before expansion was acceptable though still not complete.

The postoperative course was satisfactory. At the end of twelve days breath sounds were normal and from the time of surgery no chyle could be recovered from the chest and none leaked from the neck incision.

DISCUSSION

It is not the purpose of this paper to review the literature of traumatic chylothorax. Recent reviews by Baldridge and Lewis (1948), Meade, Head, and Moen (1950), Hoffman, Ivins, and Kern (1952), and Goorwitch (1955) adequately cover the subject. However, several points in the treatment of traumatic chylothorax bear emphasis.

Anatomy.—It is important that the surgeon who treats traumatic cases or operates in the mediastinum or neck should be aware of the possibility of injury to the thoracic duct and be cognizant of the general anatomy of its course. The thoracic duct enters the chest through the aortic hiatus of the diaphragm and ascends between the azygos vein and the aorta on the anterior surface of the vertebrae. Baldridge and Lewis[1] found a single thoracic duct in each of twenty bodies studied. Van Pernis,[30] in a study of 1,081 bodies, found a similar uniformity within the chest. Variations in the upper portion were present in that in 892, or 82 per cent, the combined or main thoracic duct crossed anterior to the subclavian artery, but posterior to it in the remainder. The duct was always anterior to the vertebral artery and vein and the thyrocervical trunk, passing in front of the phrenic nerve and medial to the scalenus anticus muscle. Termination was in the angle formed by the junction of the left subclavian and left internal jugular vein or within 1 cm. of the angle. Meade, Head, and Moen[21] reported a single duct in 78 per cent of 135 cadavers studied. In 17 per cent there was a short, single duct which divided into two and united just below or above the diaphragm. A single duct which divided into two and ran through the chest was found in 5 per cent. From these studies it is apparent that localization of the duct in its lower portion above the diaphragm or at its termination in the angle formed by the junction of the left internal jugular vein and left subclavian vein should not give untoward difficulty to the surgeon.

It is the loss of chyle itself which produces the remarkable and rapid changes in the patient. Jahnsman[13] lists the characteristics of chyle as follows: (a) milky appearance, (b) creamy layer on standing, (c) finely emulsified,

with fine fat globules, (d) no odor or an odor corresponding to that of the food eaten, (e) alkaline reaction, (f) specific gravity exceeding 1.012, (g) constant degree of opalescence, (h) sterile and resisting putrefaction, (i) fat content generally high, 0.4 to 4 per cent, and like fat in food, (j) total solids generally greater than 4 per cent, (k) total protein generally exceeding 3 Gm. per 100 c.c., ranging from 1 to 6 Gm., (l) salts and organic substances approximating the values found for chyle from the thoracic duct, and (m) fat droplets microscopically. Chyle takes the Sudan III stain as well and Hodge and Bridges[11] have pointed out that the nonprotein nitrogen, sugar, urea, and minerals are similar in amount to those found in the blood stream. Sixty to seventy per cent of the absorbed fat is present in the thoracic duct chyle.[12] The loss of this protein-rich, fat-rich food produces the patient's inanition and dehydration and, if uninterrupted loss continues, his death.

Diagnosis.—The diagnosis of chylothorax is essentially based on the aspiration of characteristically milky-appearing fluid from the chest. In the ordinary traumatic case the presence of a hemothorax may at first obscure the chyle but with succeeding aspirations the fluid changes in color from "sanguinopurulent" to "milky." The earliest impression may be that empyema is present but cultures will be negative and Lampson[16] has demonstrated the bacteriostatic character of chyle. Concomitant with the loss of chyle, the patient's nutrition suffers remarkably rapdily, and a downhill course is started which ends in death unless spontaneous or surgical closure of the chylous fistula ensues.

Early Treatment.—The early treatment should be directed toward the maintenance of the patient's nutrition by intravenous plasma, blood, aminoacids, and electrolytes as indicated by the patient's course. A high protein-low fat diet should be given. All efforts should be directed toward replacing the great amount of protein and fluid lost in the chyle. The hypoproteinemia and dehydration resulting from a chylous fistula occur rapidly and are difficult to offset if the fistula persists. The intravenous administration of the patient's own aspirated chyle would appear to be the ideal form of therapy in conservative management. This would hold true if it were not without danger. There have been both successes and failures in its use. Little, Harrison, and Blalock[17] returned 22 L. of chyle intravenously to a patient without mishap. Touroff[29] reported 2 such cases with aspiration of the chyle from the thorax and immediate intravenous return to the patient, successfully in each instance. Whitcomb and Scoville's[31] patient died suddenly after the administration of a small amount of refrigerated, citrated chyle. The death reported by Peet and Campbell[23] occurred suddenly during surgery. No cause was found. Intravenous chyle and intrasternal chyle had been given. There is little to be learned from these conflicting reports except that the use of intravenous chyle is not without risk. With safer methods of therapy available, the use of intravenous chyle should not be employed until investigation has demonstrated under what conditions it may be used with impunity.

The chest should be kept free of chyle by aspiration. If the chylothorax perists, a large caliber catheter should be introduced into the thorax and connected to a water trap and suction used. Measures such as phrenic crush,

pneumothorax, thoracoplasty, x-ray therapy, and the like appear now to be of historical interest only. It is important that the conservative measures employed be pressed with the utmost vigor, for almost one-half of the cases reported since 1948 did respond to nonsurgical measures with healing of the fistula and recovery (14 cases; 12 recoveries).

From a study of the literature there appears to be no way of predicting which case will respond to conservative management and which will not and thus will require surgical ligation of the duct. The two factors which should logically be of importance are first, the rate and amount of chyle loss suffered by the patient, and second, the patient's response to conservative management. While the rate of chyle loss and the amount of chyle undoubtedly bear direct relationship to the patient's response to conservative therapy, it is clinically more realistic to judge the necessity for surgery on the patient's general condition rather than on the measured amounts of chyle loss per day. It is apparent that the majority of those who have treated traumatic chylothorax by surgical ligation of the duct have first employed conservative measures until it was obvious that nutritional or intrathoracic complications demanded surgical intervention.

Surgical Therapy.—Studies of the anatomy of the thoracic duct have demonstrated that surgical ligation is most easily performed at the level of the diaphragm through a right thoracotomy incision.[30] When a right-sided chylothorax is present, the therapeutic approach is obvious. In the presence of a left chylothorax, a left thoracotomy approach should be employed if complications of the chylothorax or the original injury are present and require correction. On the other hand, if repeated aspiration has indicated no need for decortication in a left chylothorax, the easier right thoracotomy approach may be used as Klepser[14] and Goorwitch[10] have emphasized. In the case reported here there was no preoperative intention of opening the thorax. It was felt that the left lung would expand, once the flow of chyle had been terminated. The necessity for opening the left chest arose during surgery and it became apparent then that decortication was necessary.

Experiences with the expandibility of the lung in chylothorax have varied. Meade and associates[21] found an encapsulated lung after nine weeks of chylothorax but no definite visceral "peel." Decortication was difficult and reexpansion was incomplete. This was similar to our experience. On the other hand Klepser[15] reported no peel over the lung despite the six to nine months the lung had been down. Expansion occurred without difficulty. One may infer not only from the experience gained from surgically treated cases, but from those treated without operation, that expansion of the lung will occur when the flow of chyle ceases. The occasional exception must be treated by decortication. In both Meade and associates' case and in the case reported here, it is likely that expansion would have occurred despite the operative findings of a trapped lung without peel; for in both instances tedious decortication did not produce fully expanded lungs; full expansion occurring in the postoperative period when the pressure and/or "irritative" effects of the chyle had been removed by ligation of the thoracic duct.

In Goorwitch's recent review,[9] the cases of chylothorax complicating injury to the cervical portion of the thoracic duct numbered 6, including his own. The case recorded here is the seventh case of chylothorax complicating cervical thoracic duct injury. Of the 7 cases, 6 were due to penetrating trauma. The rarity of reports of this type of injury is due to the close relationship of the thoracic duct to the major neck vessels; trauma in this area more often leads to laceration of major blood vessels and death than to isolated cases of injury to the thoracic duct. One case of this group followed a left radical neck dissection with injury to the thoracic duct.[8] Bilateral chylothorax resulted due to rupture of the mediastinal pleura by the chyle descending in the visceral compartment. These authors felt that this complication occurs more often than is known or reported. Certainly injuries to the thoracic duct during surgery in the left neck are common enough. I have twice ligated the cervical portion of the duct following inadvertent surgical injury during neck dissection. Logically enough chylothorax would not occur unless first, the injury to the duct had been overlooked during surgery, and second, external drainage proved to be inadequate. Chylothorax should remain a rare complication of neck surgery.

Therapy in the cases recorded by Goorwitch was pressure over the draining neck wound and thoracentesis in two cases[8, 16]; thoracentesis followed by ligation of the thoracic duct in the neck in two cases[16, 24]; thoracentesis followed by ligation of the thoracic duct within the chest in two cases[9, 14]; and in the author's case ligation of the thoracic duct in the neck with concomitant left thoracotomy.

Surgeons who must treat a chylothorax resulting from trauma to the cervical portion of the thoracic chest should perform ligation in the neck when the wound is recent and other neck pathology requires correction. If it is apparent that decortication of the lung may be required, the duct should be ligated in the chest, or the neck and chest may be explored separately at one operation or as staged procedures with ligation of the thoracic duct performed in the first operation. With a healed neck wound and an unexpanded lung, ligation of the thoracic duct may be performed in the chest following decortication as Goorwitch reported.[9]

In the light of present surgical experiences it is apparent that surgical ligation of the thoracic duct is curative and is without mortality in the cases reported since 1948. Conservative measures as outlined should be employed initially but should be abandoned before patient deterioration appears. If, on repeated thoracentesis, the chyle fistula persists, surgical correction is warranted and safe.

SUMMARY

The eighteenth successful surgical ligation of the thoracic duct for traumatic chylothorax is reported. Ligation of the thoracic duct was performed in the neck. The conservative and surgical methods of therapy are outlined. It is emphasized that since the first successful ligation of the thoracic duct in the chest by Lampson surgical correction of traumatic chylothorax, as reported,

has been uniformly curative and without mortality. It is important that surgical ligation of the thoracic duct be performed before patient deterioration due to the loss of chyle appears.

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LIPOMA OF THE ESOPHAGUS

Report of a Case

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LIPOMAS of the esophagus are rare lesions which are important to differentiate from the more common malignant tumors because of their excellent prognosis if properly treated in the early stages of the disease. The infrequency of occurrence of these tumors is indicated by Buckstein's report[2] that the records of Bellevue Hospital revealed no case of esophageal lipoma in the thirty-year period ending with 1935. So far as we have been able to determine, the first reported case is that of Vinson[15] in 1922. His patient had a long, pedunculated, submucosal lipoma which caused intermittent symptoms and grew to such length that it protruded several inches from the mouth when it was expelled from the esophagus by vomiting; it was successfully excised by a transcervical approach. Since this report only a few additional cases of esophageal lipomas have been recorded in the literature (Table I). The case to be presented is interesting not only because of the rarity of the condition but also because it was

Table I. Summary of Cases of Lipoma of the Esophagus Reported in the Literature

Author	Year	Type of Lesion	Location	Symptoms	Treatment
Vinson[15]	1922	Pedunculated	Upper third	Regurgitated tumor	Excised (transcervical)
Tobler[13]	1922	Sessile	?	None	Incidental autopsy finding
Garretson and Hardie[3]	1928	Pedunculated	Upper third	Regurgitated tumor	Excision (transoral)
Weyrich[16]	1933	Pedunculated	Upper third	Regurgitated tumor; asphyxia	Asphyxiated by tumor
Kramer[7]	1934	Pedunculated	Upper third	Throat irritation; regurgitated tumor	Excision (transoral)
Milanes[8]	1939	Sessile	Lower third	None (Hiatus hernia symptoms)	Esophagoscopic biopsy
Harrington and Moersch[5]	1944	(1) Pedunculated	Upper third	Dysphagia; tumor regurgitation	Excision (transthoracia)
		(2) Pedunculated	Upper third	Tumor regurgitation	Excision (transoral)
Kinnear[6]	1955	Large polypoid	Lower half	Dysphagia	Excision (esophagectomy)
Ochsner and Ochsner	1956	Small polypoid	Lower third	Dysphagia; pain	Excised (transthoracic)

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situated in the lower third of the esophagus, was producing symptoms, was misdiagnosed by both roentgenologic and endoscopic examiners, and was successfully removed by simple excision.

SYMPTOMS

Totten and co-workers[14] presented an extensive review of the literature on benign esophageal cysts and tumors in 1953. Aside from the dramatic occurrence of regurgitation in about 50 per cent of polypoid tumors, the symptoms were found to be readily grouped into 3 categories: Gastrointestinal symptoms, chiefly some type of dysphagia, or occasionally regurgitation, vomiting, anorexia, or loss of weight, occurred in about 75 per cent of the cases; pain, varying from slight retrosternal or epigastric discomfort to sharp radiating pain, occurred in about 40 per cent; respiratory symptoms, such as cough, dyspnea, and wheezing, were present in about 25 per cent of the patients. Hemorrhage occurred in only 2 patients, neither of whom had lipomas.

ROENTGENOLOGIC DATA

As described by Schatzki and Hawes[12] and Harper and Tiscenco,[4] the roentgenologic appearance of extramucosal, intramural tumors of the esophagus is based on the fact that the lesions are closely associated with the esophageal wall and the mucosa is stretched over them. Passage of the barium through the esophagus is not delayed, despite the apparent filling defect. The barium column may split over and channel around the tumor where it projects into the lumen. In profile this filling defect shows an abrupt margin where it protrudes into the barium filled lumen of the esophagus. In a frontal view, the edge of the lesion is sharply outlined. The mucosa over benign esophageal tumors is not destroyed and rarely becomes ulcerated. It stretches as the mass enlarges. The thinned rugate folds may show a divergence over the smooth mass or may be merely flattened by the submucosal expansion of the tumor. A pedunculated tumor, being mobile on its pedicle, may show a variation of its position in the esophagus, or the pedicle itself may be demonstrable.

Schatzki and Hawes[12] stressed the need of careful fluoroscopy and precise spot filming in the demonstration of these features. They indicated also that the use of too much barium in filling the esophagus may obscure the fine diagnostic details, whereas the use of too little barium will result in inadequate filling and incomplete demonstration of the lesion. The necessity of visualizing the area in multiple projections was clearly shown.[12]

Benign intramural esophageal tumors are usually oval or spheroid, usually smooth but at times lobulated, and may appear as a soft tissue mass, intraluminal or extraesophageal, at the location of the defect in the barium column. Since it is known that fatty tissue is more radiolucent than other soft tissues, a lipoma may be specifically suspected if the soft tissue tumor seems unusually radiolucent for a mass of the size visualized.

Harper and Tiscenco[4] discussed the numerous pathologic processes in the mediastinum which may cause pressure on the esophagus and require differ-

ential diagnosis from benign esophageal tumors. In brief, the commonest differential problems are esophageal carcinoma, mediastinal cysts or tumors, and aneurysms of the thoracic aorta or its primary branches.

TREATMENT

The treatment of esophageal lipomas is surgical. Each case should be studied by esophagoscopy in order to localize the lesion precisely, to visualize the pedicle if one is present, to visualize the mucosa in the area of the lesion, and to obtain a biopsy if possible. A pedunculated tumor may occasionally be

Fig. 1.—Roentgenogram showing polypoid filling defect in lower third of esophagus.

removed by an endoscopic snare, as Garretson and Hardie[3] pointed out. Otherwise, a transcervical or transthoracic approach is necessary for removal. Careful appraisal of the esophageal mass may indicate that it may be benign and simple enucleation may be possible without breaking the mucosa. This procedure was accomplished in the case to be presented. Larger or more complex tumors,

even though benign histologically, may require partial esophagectomy, as in the case reported by Kinnear.[6] The necessity for prompt treatment once these tumors are recognized should be stressed. Weyrich[16] described a pedunculated lipoma which was expelled from the esophagus and asphyxiated the patient by occluding the opening to the larynx.

CASE REPORT

C. F. J., a retired Texas farmer, aged 67 years, was admitted to Ochsner Foundation Hospital on Feb. 1, 1950. Four years previously, he began to have occasional attacks of nausea. For two years he had been aware of intermittent episodes of food "sticking" low down in his chest while eating; these attacks would prevent him from finishing his meal. Two

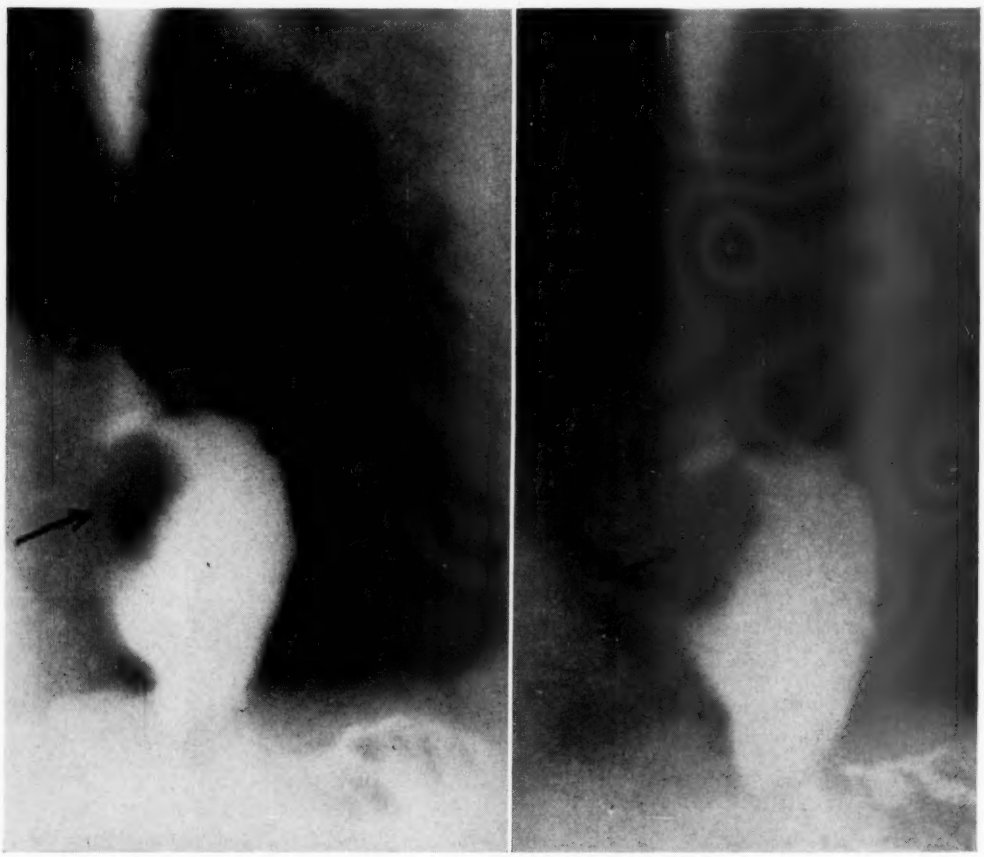

Fig. 2.—Roentgenograms made by spot-film technique reveal the sharply defined margins of the submucosal lipoma protruding into the lumen of the esophagus.

days before admission, while he was eating steak, food again seemed to "stick" in his chest and a severe, sticking, subxiphoid pain developed. This was relieved by vomiting, but it recurred when he swallowed more food. His local physician promptly referred him to the hospital for surgical treatment.

On admission the patient was having no pain, as it had been relieved by morphine. He had had no symptoms suggesting angina pectoris, had noticed no hematemesis or melena, and had lost no weight. His wife had noticed a pronounced change in the patient's personality

in the past several years manifested by suspiciousness, sloppy and careless behavior, and alternate episodes of anger and apathy. A neurologic consultant attributed this to cerebral arteriosclerosis.

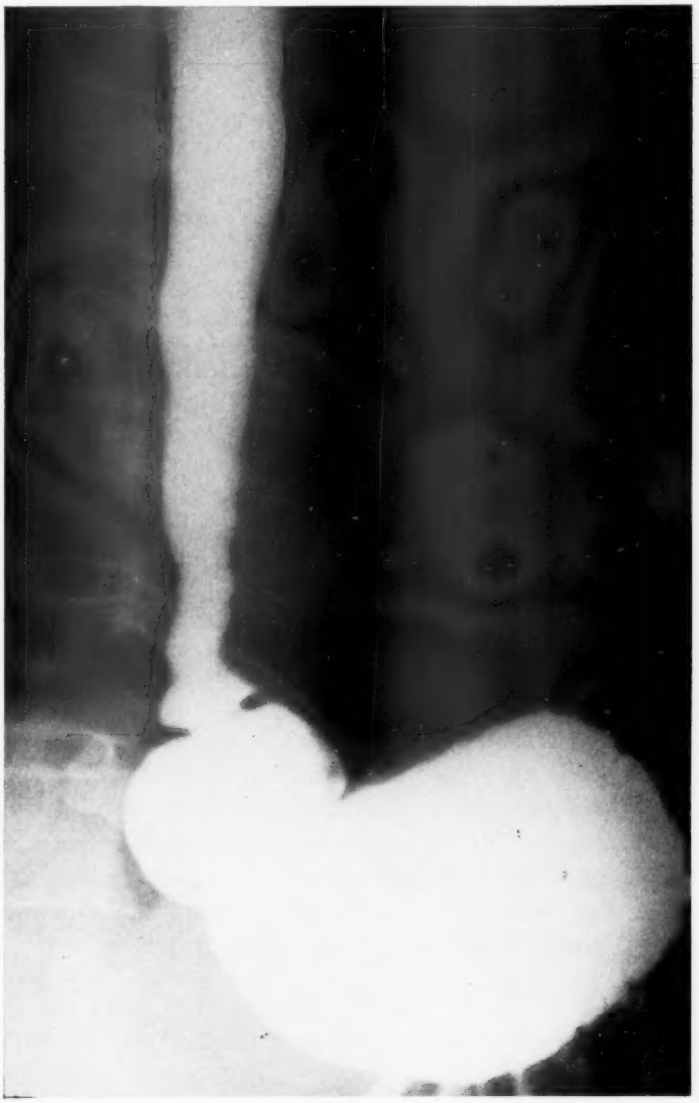

Fig. 3.—Roentgenogram made postoperatively shows a normal esophagus. A small hiatus hernia had developed.

Physical examination disclosed no abnormality other than mild pulmonary emphysema. Roentgenologic examinations of the chest, gall bladder, and colon showed no abnormalities. Fluoroscopic study of the upper gastrointestinal tract on Feb. 3, 1950, revealed a small niche along the margin of the lower esophagus about 5 cm. above the hiatus. Some irregularity of the esophageal wall and mild spasm of the lower esophagus were noted. The fluoroscopist thought this indicated a benign esophageal ulcer, but the roentgenograms gave evidence of a polypoid filling defect in addition to the ulcer (Figs. 1 and 2). The roentgenologic diagnosis was ulcerative carcinoma in the lower third of the esophagus.

On Feb. 7, 1950, under general anesthesia, endoscopy revealed an indurated, constricting lesion of the lower part of the esophagus near the esophagogastric junction which the esophagoscopist thought was carcinoma of the esophagus. Histologic examination of the specimen obtained at biopsy showed only subacute inflammation.

About four hours after esophagoscopy, some soft tissue emphysema of the upper anterior chest and base of the neck was noted. This was associated with considerable pain in the epigastrium, substernal area, and anterior aspect of the neck. A roentgenogram of the chest indicated the presence of extensive mediastinal emphysema as well as subcutaneous emphysema of the neck. There was no pneumothorax. The patient's condition did not improve and cervical mediastinotomy was performed on Feb. 8, 1955. Within three days the emphysema had completely resolved, and the patient was then prepared for exploration, the provisional diagnosis being carcinoma of the esophagus.

On Feb. 17, 1950, the abdomen was first explored in order to be sure that the neoplasm did not extend to the liver or infradiaphragmatic portion of the esophagus. No evidence of metastases being present, the incision was then extended across the costal margin into the left sixth intercostal space. Following opening of the thorax, examination of the esophagus showed none of the anticipated induration. There was a soft bulbous swelling in the wall of the lower esophagus which felt like a lipoma. The muscularis of the esophagus was divided and a submucosal lipoma excised. No mucosal lesion was evident after removal of the lipoma. To check this, an opening was made in the stomach, a finger introduced, and the lower esophagus carefully palpated through the cardioesophageal opening. The excised tumor, a benign lipoma, weighed 5 Gm.

Recovery was prompt and the patient was discharged on the tenth postoperative day. When examined fifteen months later, he was in good health and the esophagus appeared normal on roentgenologic examination (Fig. 3).

SUMMARY

A case of lipoma of the esophagus, believed to be the tenth to be reported, has been presented. The tumor was submucosal, in the lower third of the esophagus, and produced definite symptoms. It was misdiagnosed by the roentgenologist and the endoscopist who examined the patient. Following endoscopic biopsy of the esophagus, severe mediastinal emphysema resulted which required cervical mediastinotomy. The lipoma was enucleated successfully by a transthoracic approach, and the postoperative result was excellent. This case exemplifies the fact that, in treating esophageal tumors, the surgeon must always be prepared to find a benign lesion and treat it appropriately.

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Book Reviews

CONDUCTED BY J. GARROTT ALLEN, M.D.

Chemosurgery in Cancer, Gangrene and Infections. Frederick E. Mohs. Springfield, 1956, Charles C Thomas. $13.50.

Few innovations in surgical technique have evoked as much controversy as Dr. Mohs' method of treatment of cancer. Sixteen years after his initial assault upon the established principles of surgical excision of superficial carcinomas, the author has produced a beautifully illustrated and well-documented volume describing in minute detail the technique which he has used so successfully and giving explicit end results in the treatment of many kinds of cancers that he has treated by his method in several hundred patients. Among the lesions treated are carcinoma of the larynx, recurrent carcinoma of the breast, tumors of the salivary glands, malignant melanoma, as well as some benign tumors, gangrene, and infectious processes.

The technique of "chemosurgery," as Mohs describes it, involves the application of a fixative paste to accessible lesions, allowing this material to remain in contact for 24 hours to allow permeation and chemical fixation of the underlying tissue. At the end of this time, the fixed tissue is excised. Numerous microscopic sections are made from the excised portions, ascertaining the exact location of each bit sectioned in relation to the original lesion. Those areas found to contain tumor at the depth of the section receive further application of the paste and re-excision is carried out. This process is usually repeated two or three times, utilizing frozen sections during the final stages, but there is apparently no theoretical limit to the number of staged excisions which could be carried out. According to the author, the great advantage of this method is that it permits microscopically controlled resection of tumor, thereby enabling the surgeon to conserve uninvolved tissue, and at the same time assure him that the limits of resection are sufficiently wide.

One of the most interesting sections in this book is a chapter on the "Modes of Spread of Cancer." Herein lies the fundamental rationale which guides Mohs in his application of the chemosurgical method. Using photographs, photomicrographs, and diagrams the author graphically illustrates the well-known fact that superficial lesions often extend in strands and sheets well beyond the visible or palpable limits of the tumor. Some neoplasms, he states, have an affinity for nerve sheaths, others for fascial planes; others behave in a seemingly erratic fashion. He believes the extensive use of well-prepared microscopic sections during the staged removal of tumors permits the surgeon to eradicate them in a controlled manner, rather than depending on the general principle of wide excision.

In the hands of the author, the results reported by him for his chemosurgical treatment of superficial cancers appear to have been eminently successful. The 5-year end results he reports for those lesions with which he has had the most experience—specifically, cancer of the skin, face, lip, eyelid, nose, and ear—are better than most of those obtained by most surgeons and radiotherapists. For example, in a group of 230 patients with squamous cell carcinoma of the face, scalp, and neck, 164 were followed for at least 5 years. Of this "determinate" group, 84.8 per cent were free of clinical evidence of recurrence at the end of the 5-year period. One-fourth of this group of patients had been previously treated unsuccessfully. However, for an accurate appraisal, one needs to know the exact status of the remaining 66 patients whose fate is unreported.

While the data presented are impressive, his method is not likely to enjoy universal acceptance as the treatment of choice in malignancies. As Mohs points out, chemosurgery

basically is a simple technique and easy to comprehend, but its proper use imposes a number of requirements. The operator must be very meticulous and of admirable patience. Either he must do his own pathology, or find a pathologist whose temperament is as uncommon as that required of the surgeon. And above all, both must be convinced that this lengthy, painstaking approach to the treatment of cancer is the one of choice in the primary attack upon the lesions he mentions.

Despite the controversial nature of his method, it is to the author's credit that he was willing to publish in detail his method and results which he realized might lead to personal criticism. The book itself is worthy of careful reading, although many surgeons are not likely to adopt his method nor to include it among their armamentary.

—Stanley P. Rigler

Recent Advances in Anesthesia and Analgesia. C. Langton Hewer and J. Alfred Lee. Boston, 1957, Little, Brown and Company. Ed. 8. Pp. 277, 95 ills. $8.50.

This volume is the eighth edition of a book first published in 1932 by C. Langton Hewer. The successive editions, as the title demands, are more like new books than new editions of an old one. Although the outline of the book and the chapter subjects are similar, the content is new and up to date with each printing. This edition presents only recent progress with certain procedures and ideas of the care of the patient during surgery, assuming that the reader has basic knowledge of these subjects.

In this edition Hewer is joined by J. Alfred Lee as coauthor. Dr. Lee is the author of *A Synopsis of Anesthesia,* also a well-known and useful textbook in the practice and teaching of anesthesia. Along with Dr. Hewer, he is accomplished in presenting material in as few words as possible.

In this relatively small volume (277 pages), an amazing amount of information is given. It seems no aspect of anesthesia has been neglected. In spite of the wide scope of this book the material is well organized and presented with clear, concise simplicity. Many will dispute some of the claims of the actions of certain drugs, particularly the statement that atropine causes slight drowsiness (page 3). The clinical side is emphasized but enough basic science is suggested to whet one's interest. A large and well-selected bibliography is listed at the end of each chapter to guide further reading.

The first 13 chapters deal with new drugs, apparatus, procedures, and essential surgical management for special cases, including, of course, hypothermic and hypotensive techniques and the treatment of collapse, shock, and cardiac arrest. The next 4 chapters deal with anesthesia for diagnostic procedures and the specialties of surgery, namely, lung, heart and great vessels, abdominal surgery, and obstetrics.

The last 4 chapters deal with less related subjects: "Complications of Anesthesia," "Psychological Aspects," "Charts and Records," and "Oxygen Therapy."

Much of the apparatus described is, of course, British and made in England, but in most instances an American equivalent is recognizable. For example, the Ryan nonrebreathing valve is essentially the Stephen-Slater or Digby-Leigh valve and Bourne's "Sparklets" are like Hingson's miniature cylinders for his Reserve Midget machine.

The book presents an excellent survey of progress made in anesthesia and the related management of patients during surgery and is profitable reading for surgeons and anesthetists. Selected chapters contain valuable information for oxygen therapists and surgical nurses as well.

—Geraldine Light

Surgery Principles and Practice. Edited by J. Garrott Allen, Henry N. Harkins, Carl A. Moyer, and Jonathan E. Rhoads. J. B. Lippincott Company. Pp. 1495, 623 ills. $16.00. Philadelphia, 1957.

The 4 editors of this textbook of surgery, together with other contributors from their own institutions, complemented by a few additional authors from other American Medical

Schools, have brought this large and somewhat unusual text into being. It has been 3 years in preparation—not so long a period of time for so large a volume. There are 50 chapters. Every phase of surgery is covered save ophthalmology and otolaryngology. The 4 final chapters of the text deal with specialities of gynecology, urology, orthopedic surgery, and neurosurgery.

The chapter on fractures was written by a general surgeon and an orthopedic surgeon. In this latter connection, it is interesting to recall that the text on fractures written from the Massachusetts General Hospital almost 20 years ago under the general editorship of Philip Wilson was written in large part by general surgeons, very few of whom today still continue to have a high level of interest in the surgery of osseous trauma. It would appear that in many areas of our country, the teaching of fracture repairs is being taken over more and more by orthopedic surgeons. In a recent survey of operations done in 4 states of this country, Dr. Frederick A. Coller, in a meeting of the American Surgical Association in Chicago in May, 1957, pointed out the wide disparities which exist in this country with reference to who does the surgery. In the state of Virginia, the larger number of operations considered to be major operations were done by surgical specialists, that is, by surgeons either certified by the American Board of Surgery or by the American College of Surgeons. Interestingly enough, however, in Virginia, a large per cent of the fractures were taken care of by the general practitioner.

Twenty years ago, we used to hear discussions of what constituted major and minor surgery. Today we hear less of minor surgery; and so, too, possibly with fractures and their management, time will eventually resolve which fractures need the early attention of a fracture specialist.

This monograph without question will find an important place in American Surgery. Its special aim is to reach the undergraduate students of surgery and young surgical house officers. Many a chapter in the book will serve as a useful source of basic information to both teachers and students.

One cannot peruse this volume without appreciating the enormity of the labor which went into its composition. In addition, one can detect, too, the influence of interest and experience in summarizing the accumulated knowledge within a field. He who would criticize this important contribution to surgery would be hard put to it to write a better text. As the literature of surgery and other medical specialities increases, the student, as well as his teacher, has found it increasingly difficult to keep up with the advance in his field. The undergraduate student who is faced with the task of trying to absorb the knowledge of the past as well as current information in the making is particularly aware of this difficulty. Journals have multiplied to record rapid acquisitions of information. More and more, students are yearning for syllabusses or concise texts which summarize in a more succinct manner the basic information in a subject. Yet the student and the teacher of 35 years ago will recall that Da Costa's *Modern Surgery*, written by a single author, was at least as large as this text. Those who have perused texts of an earlier age will recall that Samuel D. Gross, writing during the Civil War period of this country, wrote for the medical students of that day two volumes of surgery, each of which was almost as large as the present volume under discussion. Much of the materials of the Gross monograph have become obsolete, because new information has superseded the old. And so, too, it may well be with certain sections of the present text. Certain it is that one reason surgery has undergone partition of many sorts is that no longer can any one person expect to embrace the whole broad range of that burgeoning field.

There is much to praise and little to criticize in this informative and interesting text. No uniform pattern of treatment of subject matter has been followed by the authors. Some are very detailed in discussion and could well serve as useful sources for basic information in the particular area under consideration. There is some duplication in the text here and there, which probably adds more than it detracts from the presentation. Each author has used his own artist. The illustrative material therefore conforms to no single pattern.

I believe that this text will find wide acceptance by American students of surgery.

—Owen H. Wangensteen

The Nurse and the Outpatient Department. Audrey Windemuth. New York, 1957, The Macmillan Company. Pp. 545. $6.50.

This book, the first text written about the outpatient department and the nurses' role in it, should be welcomed by the faculties of nursing schools, by nurses engaged in outpatient work, and by nurses in hospital situations.

The contents of the book are divided into three parts. The first deals with the history of dispensaries, outpatient departments in modern medical care, the trend toward expansion of group practice facilities, and the organization of a large outpatient department as typified by the Outpatient Department of the University of Minnesota.

The second part is concerned with relationships. It is divided into chapters challengingly called "Adventure in Patient Relationships," "Adventure in Health Education," "Education in Health Team Relationships," and "Adventure in Human Relations."

The third part gives suggestions for health teaching in 12 special clinics.

The first two chapters on history and development are brief but informative. They would make good reference reading for any nurse starting to work in an outpatient department. The suggestions for health teaching, in the third part of the book, is based on a review of current medical therapy. Emphasis is placed upon the need for health teaching to be always based on the recommendations of and with the consent of the medical staff.

The greatest contribution made by the text, in my opinion, is in the second part on relationships. The author in this part gives a vision of what nurses might contribute with their skills, their understanding of patients' needs, and by a knowledge of community resources, through teamwork with doctors, the social service staff, and with the workers in all of the ancillary services. If the business of the day in clinics with few nurses and many patients interferes with reaching the goal envisioned by Miss Windemuth, it is hoped that nurses may find themselves inspired by her to strive for the first goal post, that of getting to know the patient—to humanize nursing. To do this, to quote the author, ". . . it is essential that she possess knowledge and understanding of human behavior and human relationships and that she have the ability to establish constructive, purposeful, interpersonal relationships."

Miss Windemuth has distilled the contents of her book from an intimate knowledge of outpatient activities through actual work experience and from a wide range in reading, as indicated by the reference lists at the end of each chapter. She is to be congratulated on her authorship of the first textbook for outpatient nursing, on her selection of material, and on her style of presentation.

—Grace Maushak

Calendar of Surgical Meetings

1957

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 11-13, 1957, The Cloister, Sea Island, Ga. Deadline for papers, Aug. 15, 1957. Secretary, Dr. Eben Alexander, Jr., Bowman Gray School of Medicine, Winston-Salem, N. C. Attendance at meetings by invitation only.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA. *Annual Meeting,* Oct. 31, Nov. 1 and 2, 1957, The Homestead, Hot Springs, Va. Deadline for papers, Aug. 1, 1957. Secretary, James K. Stack, 700 N. Michigan Ave., Chicago 11, Ill.

AMERICAN CANCER SOCIETY. *Annual Meeting,* Oct. 28-29, 1957, Park-Sheraton Hotel, New York City, N. Y. Participation by invitation only.

AMERICAN COLLEGE OF SURGEONS. *Clinical Congress,* Oct. 14-18, 1957, Convention Hall, Atlantic City, N. J. Secretary of the College, Michael L. Mason, 154 E. Erie St., Chicago 11, Ill.

AMERICAN MEDICAL ASSOCIATION. *Clinical Meeting,* Dec. 3-6, 1957, Auditorium, Philadelphia, Pa. Deadline for papers, July 15, 1957. Secretary, American Medical Association, George F. Lull, M.D.; Secretary, Council on Scientific Assembly, Thomas G. Hull, M.D.; address of both, 535 North Dearborn Street, Chicago 10, Ill.

THE INTERNATIONAL SOCIETY OF ANGIOLOGY. *Third International Congress,* Oct. 18-21, 1957, Ambassador Hotel, Atlantic City, N. J. Secretary-General, Henry Haimovici, M.D., 105 East 90th St., New York 28, N. Y.

INTERNATIONAL SOCIETY OF SURGERY. *Seventeenth Congress,* Oct. 20-27, 1957, City University Medical School, Mexico City. Details of hotel accommodations and reservations are being handled by "Mexamericana," Paseo de la Reforma 44, Mexico, I. D. F.

PAN-PACIFIC SURGICAL ASSOCIATION. *Seventh Congress,* Nov. 14-22, 1957. Honolulu, Hawaii. Director General, F. J. Pinkerton, M.D., Room 230, Young Building, Honolulu, Hawaii.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 10-12, 1957, Greenbrier Hotel, White Sulphur Springs, W. Va. Secretary, George G. Finney, M.D., 2947 St. Paul St., Baltimore 18, Md. Guests are invited by the Secretary at the request of the Membership.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 21-23, 1957, Hotel Utah, Salt Lake City, Utah. Deadline for submission of papers, Aug. 15, 1957. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.

1958

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS. *Annual Meeting,* April 23-25, 1958, Edgewater Gulf Hotel, Edgewater Park, Miss. Secretary-Treasurer, Dr. Wm. J. Engel, 2020 East 93rd Street, Cleveland, Ohio.

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 16-18, 1958, Statler Hotel, Boston, Mass. Secretary, Dr. H. T. Langston, 1919 West Taylor Street, Chicago 12, Ill.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 19-21, 1958, The Grove Park, Asheville, N. C. Secretary, Dr. Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C.

AMERICAN SURGICAL ASSOCIATION. *Annual Meeting,* April 16-18, 1958, Waldorf-Astoria, New York, N. Y. Secretary, Dr. William A. Altemeier, Cincinnati General Hospital, Cincinnati, Ohio.

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* April 28–May 1, 1958, Roosevelt Hotel, New Orleans, La. Deadline for submission of papers Dec. 1, 1957. Secretary, Dr. Samuel L. Raines, 188 South Bellevue Boulevard, Memphis 4, Tenn.

THE CENTRAL SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 20-22, 1958, Columbus, Ohio. Deadline for submission of abstracts, Nov. 15, 1957. Secretary, Dr. Charles D. Branch, 1002 N. North Street, Peoria, Ill.

THE HARVEY CUSHING SOCIETY. *Annual Meeting,* April 21-23, 1958, The Mayflower, Washington, D. C. Secretary, Dr. David L. Reeves, 316 West Junipero Street, Santa Barbara, Calif.

INTERNATIONAL UNION AGAINST CANCER. *Seventh International Cancer Congress,* July 6-12, 1958, London, England. Papers, dealing with new and unpublished work, must be submitted with abstract (not over 200 words) before October, 1957. Secretary General, Harold Dorn, National Institute of Health, Bethesda 14, Md.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 3 and 4, 1958, Mount Washington Hotel, Burton Woods, N. H. Deadline for submission of papers, June 1, 1958. Secretary, Dr. Richard Warren, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

PACIFIC COAST SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 3-5, 1958, Biltmore, Santa Barbara, Calif. Secretary, Dr. Carlton Mathewson, Stanford University Hospital, San Francisco, Calif.

SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 13-15, 1958, Boston, Mass. Deadline for submission of abstracts three months prior to meeting. Secretary, Dr. James D. Hardy, University of Mississippi Medical Center, Jackson, Miss.